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BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 23 1952

OBSERVATIONS ON PROLONGED CORTISONE ADMINISTRATION IN RHEUMATOID ARTHRITIS*

BY

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In a preliminary study of the therapeutic effects of cortisone and other steroid substances in rheumatoid arthritis, certain methods of objective assessment by which relatively small clinical variations can be detected were described (Copeman *et al.*, 1950). The application of these methods to a further series of patients with active rheumatoid arthritis under treatment with cortisone for longer periods is the subject of the present report.

We have been mainly concerned in devising a suitable method of administration which will suppress the disease indefinitely and enable the patients to resume useful and independent lives, free from unpleasant side-effects. Haematological and metabolic changes occurring during routine administration of cortisone were investigated, and such side-effects as did occur in this small series were studied in detail.

Selection of Patients

The patients selected had suffered from active and undoubted rheumatoid arthritis for at least six months, and in most cases much longer, as shown by the clinical signs and a raised erythrocyte sedimentation rate. They were all regarded as "severe cases," since they could not carry out their normal occupation and had already become dependent on others. They described themselves as "crippled," though, since the joint changes as studied radiologically were often minimal, much of their disability was potentially reversible.

Each of the 20 cases was observed for at least three months. Thirteen have been examined in detail by the methods of assessment previously described, with the addition of a finger-ring test (Hart and Clark, 1951), and concurrent metabolic studies. The remaining seven patients, who provided their own cortisone, were placed in the same clinical category, though they were submitted to a less extensive metabolic study. The length of study under continuous administration was as follows:

Months:	3	4	5	6	7	8	9	10	Total
No. of cases ..	1	3	4	3	6	1	1	1	20

Dosage Schedule

On the assumption that cortisone does not cure rheumatoid arthritis but only suppresses the disease (Hench, 1950), it was decided that as soon as the symptoms had been relieved adequately the dose should be lowered to a level at which this improvement might be maintained for a prolonged period without the appearance of undesirable reactions. Such a scheme has recently been favourably reported on by Boland (1951), who studied a much larger series for a longer period. Our dosage schedule therefore consisted of the following three phases: a period of initial high (suppressive) dosage; a period of gradual reduction of dosage; and a period of minimal (maintenance) dosage.

In most cases cortisone has been given by intramuscular injection during the first two periods (initial suppression and reduction of dosage). When the minimal maintenance level has been found the oral route was used. In this way we were able to compare the relative effectiveness of muscular and oral administration; furthermore, it was much more convenient for out-patients to take the compound by mouth.

*This study was aided by grants from the Medical Research Council, the Empire Rheumatism Council, and the Dan Mason Research Foundation of the West London Hospital Medical School.

Initial Suppressive Dosage

Two initial dosage schemes have been studied: (1) The "classical" method described by Hench, Kendall, Slocumb, and Polley (1949) in their original report—namely, 300 mg. on the first day, 200 mg. on the second, 150 mg. on the third, and subsequently 100 mg. daily; and (2) 100 mg. daily from the first day onwards. Doses of more than 100 mg. were divided into two injections, whereas 100 mg. and below was given once a day.

A daily dose of 100 mg. has been given until the patient has improved enough to lead a comfortable life and to have a reasonable prospect of returning to work. This level of improvement is assessed by the methods already described, which are based on disappearance of pain and tenderness and performance of functional tests (Copeman *et al.*, 1950). If possible, the patients leave the hospital for a day or two to test their functional capacity in their home surroundings.

Ten patients have been treated according to scheme 1 and 10 patients according to scheme 2. It is our impression that the lower dosage is sufficient and gives a smoother response, though there may be no measurable improvement for five to seven days.

"Boost" Dosage.—In our recent cases we have given a higher dose—200 mg. a day for 7 to 10 days—at the "comfortable" stage, which usually develops 14 to 21 days after treatment has begun, in order to obtain further improvement. Increasing experience with the "classical" initial dosage scheme has led us to the conclusion that, despite dramatic loss of pain and tenderness, patients who had often been "crippled" for months might be unable to take full advantage of the improvement owing to their prolonged relative immobility, and that they tended to develop pains due to muscular strain. By giving the "boost" dosage for a short time after the patients had been rehabilitated and had been free from pain for two weeks or more we frequently obtained a further gratifying degree of improvement.

Period of Gradual Reduction of Dosage

At a stage when the disease process seems to be satisfactorily under control the daily dose is reduced by 12.5 mg. (0.5 ml.) at a time. During this stage we find that careful methods of assessment are most important, as it is only in this way that the lowest maintenance dose can be found. The patient, knowing the dose is being reduced and fearful of relapse, will tend to exaggerate minor changes. Originally the dose was reduced every two or three days, but this proved to be too rapid, and dose reduction every five to seven days seems to be more satisfactory. The daily dose is raised by 12.5 mg. or more on changing over to oral administration, since, as other workers (Boland and Headley, 1951) have found, oral dose requirements are slightly larger. Eventually the oral dose is lowered in the same way as described for diminution of the intramuscular dose.

Maintenance Dosage

Because most cases of rheumatoid arthritis will require prolonged treatment with cortisone, as low a maintenance dose as possible must be found. Although this may need to be increased temporarily during periods of physical and mental stress, it will remain effective in most cases for prolonged periods without relapses occurring, and may even in some cases be further diminished as time goes on.

When the oral maintenance dose has been established the patient is discharged from hospital, encouraged to return to his normal duties, and asked to attend once a week for clinical and haematological assessment.

Oral Dosage.—The relative effectiveness of intramuscular and oral maintenance doses is subject to individual variations. In some cases the difference between the two is not more than 25 mg. a day. In at least one case (Case 7) the response seemed to be actually better when the drug was taken by mouth. In Case 6 it was impracticable to administer the drug intramuscularly as the patient was having a large dose of insulin at the same time. We have used "cortone" tablets in a few cases, but most of the oral administration has been in the form of the aqueous crystalline suspension produced for intramuscular injection, which is satisfactory except for its obnoxiously bitter taste, to which most patients become accustomed. We recommend that the dose should be measured accurately with a syringe into a spoon; in view of the tendency of the crystals to adhere to the sides of glass great care should be taken that none of the dose is wasted.

Clinical Assessment

The methods of assessment which we have previously described have provided a satisfactory means of controlling the dosage of cortisone. We now rely on them to a much greater extent than on metabolic or pathological investigations, including even the sedimentation rate. The methods as described are rather laborious for day-to-day clinical use, so that the full joint chart and set of functional tests are now completed only from time to time, six or seven representative joints and tests being chosen for day-to-day assessment.

Of the tests described, joint tenderness continues to correlate accurately with the clinical state. We are less impressed with the tests involving the study of the range of movement of individual joints—unless, as in the knee-joint, the range can be accurately measured between two fixed points—because the increase in range of movement is either too obvious to need measuring, or, if it is slight, measurements are not accurate enough to eliminate the error due to subjective bias on the part of the assessor.

We find the grip test particularly useful if the fingers, hands, or wrist-joints are involved. Similarly, the ring-size test is an accurate and objective measurement of the swelling in the interphalangeal joints.

Where stiffness is a prominent feature, tests involving speed of movement—for example, the speed with which the arms can be "flailed" or lifted vertically above the head in a fixed period of time, usually 15 seconds—are especially useful. Where the lower limbs are predominantly involved the rheumatoid "flop" disappears early in treatment and its study is of little use in assessing progress in the later stages; but the ability to stand on a chair without holding on, to kneel, and to lie on the ground and get up without help, or—in bedridden patients—the speed at which they can flex and extend their knee-joints, are all satisfactory tests.

In general it is important to choose the tests individually for each patient according to his particular disabilities. No single quota of tests can possibly be satisfactory if indiscriminately used.

Results

Of the 20 patients treated, improvement was graded as good in 12 cases (fully employed in normal work and able to undertake normal recreation and normal housework); fair in 5 cases (fully employed in light work—limited recreation and all but heaviest housework); and definite but poor in 3 cases (unemployable—limited physical activity—light housework).

Table I shows that cortisone treatment has enabled 17 of the patients chosen for this study to leave hospital and resume their previous work or, in the case of the women, carry out normal housework. In three patients the results were disappointing. In one (Case 4) we were unable to find a maintenance dose low enough to avoid adverse effects. In the other two (Cases 16 and 19) permanent joint damage was too severe for the patients to become independent of help.

In Case 1 cortisone appeared to induce a complete clinical remission which has lasted so far for eight months. In spite of this the patient has had a persistently raised sedimentation rate, suggesting that the condition is latent and not cured.

The maintenance dose necessary to keep a patient comfortable varies considerably from case to case, but the

requirements of any single individual fall within a small range—for example, 25 mg. We have not seen the type of case reported by Boland (1951), in which maintenance requirements fluctuated wildly and inexplicably. No case has so far become refractory on prolonged administration. We have not been able to determine any factors which will enable us to predict in advance whether a patient will need a high or a low maintenance dose. As our cases were chosen from those showing the disease in a highly active condition, though the permanent deformity was not extensive, we are unable to correlate dosage with the duration of the disease, but our results do not suggest that there is a significant relationship between dosage and the degree of activity of the disease as judged on a clinical and haematological basis.

TABLE I.—*Results*

Case No.	Age and Description	Clinical Assessment and Duration of Disease	Initial Dose High or Low	Maintenance Dosage (mg.)		Result
				I.M.	Oral	
1	Married woman aged 50. Housework	Rheumatoid arthritis 2 years. Unable to run house or carry anything for 11 months. Walked 100 yards with difficulty. Wakened every night by pain	High	37·5	37·5	After 3 weeks' administration was able to return home and lead a normal life, including housework. Cortisone gradually reduced, and stopped after 6 months. No signs of relapse 7 months after suspending administration
2	Unmarried woman aged 55. Company secretary	R.A. 4 years. Unable to work for 2½ years. Walked ¼-mile slowly. Continually wakened by pain. Large synovial swellings on dorsum of both wrists and knees	High, and "boost" dose of 200 mg./day for 4 days on 98th day and 5 days on 134th day	75	70	Able to resume full-time secretarial work 6½ months after starting administration. Successfully ran her own flat for 4 months. This patient was found dead in her flat on 8/8/51, having been at work the previous day. Necropsy (Dr. Keith Simpson) revealed a massive intracerebral haemorrhage
3	Married woman aged 34. Housework and 3 children	R.A. 16 months. Light cooking; nothing else. Wakened ½-hourly by pain for 2½ years	High, and "boost" dose of 200 mg./day for 13 days on day 101	75	87·5–100	Able to lead a completely normal life, including housework, care of children, shopping, while under administration. Knees relapsed rapidly whenever dosage was cut to below her maintenance dose; the rest of her joints retained their improvement
4	Married woman aged 38. Housework and child	R.A. 20 months. Unable to dress herself or do housework for over a year. Could shuffle only 300 yards. Had not slept well for 18 months. Could not get into a bath	High, and "boost" dose of 200 mg./day for 6 days on day 40 and 7 days on day 84	75	100	Able to run her home and look after her child and do light gardening. Administration suspended because of side-effects. Rapid relapse
5	Married woman aged 46. Housework and child (Figs. 1 and 4)	R.A. 5 years. Rapid deterioration in last 3 months. Able to do only very light housework. Continually wakened by pain	Low	62·5	80	Can lead a normal life as a housewife
6	Army officer aged 31. Married	R.A. 2½ years. Partly bedridden; with great difficulty could walk 30 yards. Unable to dress or climb stairs. Wakened for 6 months nightly by pain	Low	75–100	75–100	Starting training as a telephone operator. Can travel independently
7	Married woman aged 34. Housework	R.A. 9 years. Permanent flexion deformity in one knee. Could walk only 100 yards. Unable to dress herself or get into a bath. Unable to run her home	High, and "boost" dose of 200 mg./day for 10 days at day 14	100	100	Can carry out all domestic duties except those involving kneeling; runs her home by herself, which she has not been able to do for years. Able to go out visiting and to theatres
8	Married woman aged 40. Housework	R.A. 2 years. Could walk only ¼ mile very slowly. Unable to do her own hair for 5 months. Could not get into bath or climb stairs	Low, and "boost" dose of 200 mg./day for 10 days at day 21	100	100	Symptomless on high dose, but gets side-effects. Comfortable but not symptomless on lower dose
9	Married man aged 44. Superintendent water inspector (Fig. 2)	R.A. 12 years. Rapid deterioration in last 2 years. Unable to work	High	50	62·5	Has returned to full employment. Work involves much travelling, walking, stair-climbing. Completely free from pain and tenderness
10	Unmarried woman aged 32. Clerk	R.A. 5½ years. Unable to work for the past 18 months. Could walk only ¼ mile slowly and with a limp. Could not get into a bath	Low, and "boost" dose of 200 mg./day for 15 days on day 14	25		Apart from her wrist-joints, which are permanently deranged, she can lead a normal life. Can do only light clerical and housework because of her wrists
11	Married woman aged 38. Housework and child	R.A. 26 months. See Case 4. Entire relapse within month of stopping treatment. On objective tests was significantly worse than on previous occasion	Low	100	100	Can do housework and look after child, light gardening, and shopping. Still discomfort on overexertion
12	Married man aged 34. Civil servant	R.A. 9 months. Could only dress himself slowly and incompletely. Had not slept well for 9 months. Unable to climb stairs or get into a bath	Low, and "boost" dose of 200 mg./day for 13 days on day 16	62·5	75	Returned to work. No pain or analgesics. Able to dress completely at normal speed. Sleeping well
13	Married woman aged 37. 3 children. Housework and 1 child to look after	R.A. 4½ years. Cannot dress herself. Help required to do stairs. Wakened by pain during the night	High	50	50	Able to do housework and take part in family life—dancing a little and light gardening
14	Married woman aged 59. Household duties	R.A. 8 months. Febrile. Swelling and pain in interphalangeals, wrist, knees, and feet. Confined to bed with pain	Low	75	50	Free from pain and able to live a slightly restricted but normal life
15	Business man aged 46	R.A. 6 years. Had to give up attending his business. Could barely walk	High	75	50	Walks slowly with some pain, but can get to his work
16	Business man aged 50	R.A. 10 years. Could get about only with difficulty; in constant pain	Low	50	50	Can walk without a stick. Some permanent deformity in hands. Can work only part-time
17	Unmarried woman aged 41. School-teacher	R.A. 3 years, interfering intermittently with her work as a teacher. Faced with possibility of permanent inability to continue working	,,	50	50	Able to return to work
18	Married woman aged 27. Housework and 2 children	R.A. 9 years. Gradual deterioration in last 3 years. Barely able to look after herself and children. Unable to do housework. Walked with a stick	,,	62·5	75	Able to lead a normal life
19	Unmarried woman aged 35. Independent means	R.A. 9 years. Ankylosis of right knee. Chair-bound	High	50	50	Able to walk without sticks. Less rest pain
20	Business man aged 66	R.A. 1 year. Practically bedridden and able to attend to his business only intermittently	,,	100	100	Able to return to work after 2 months

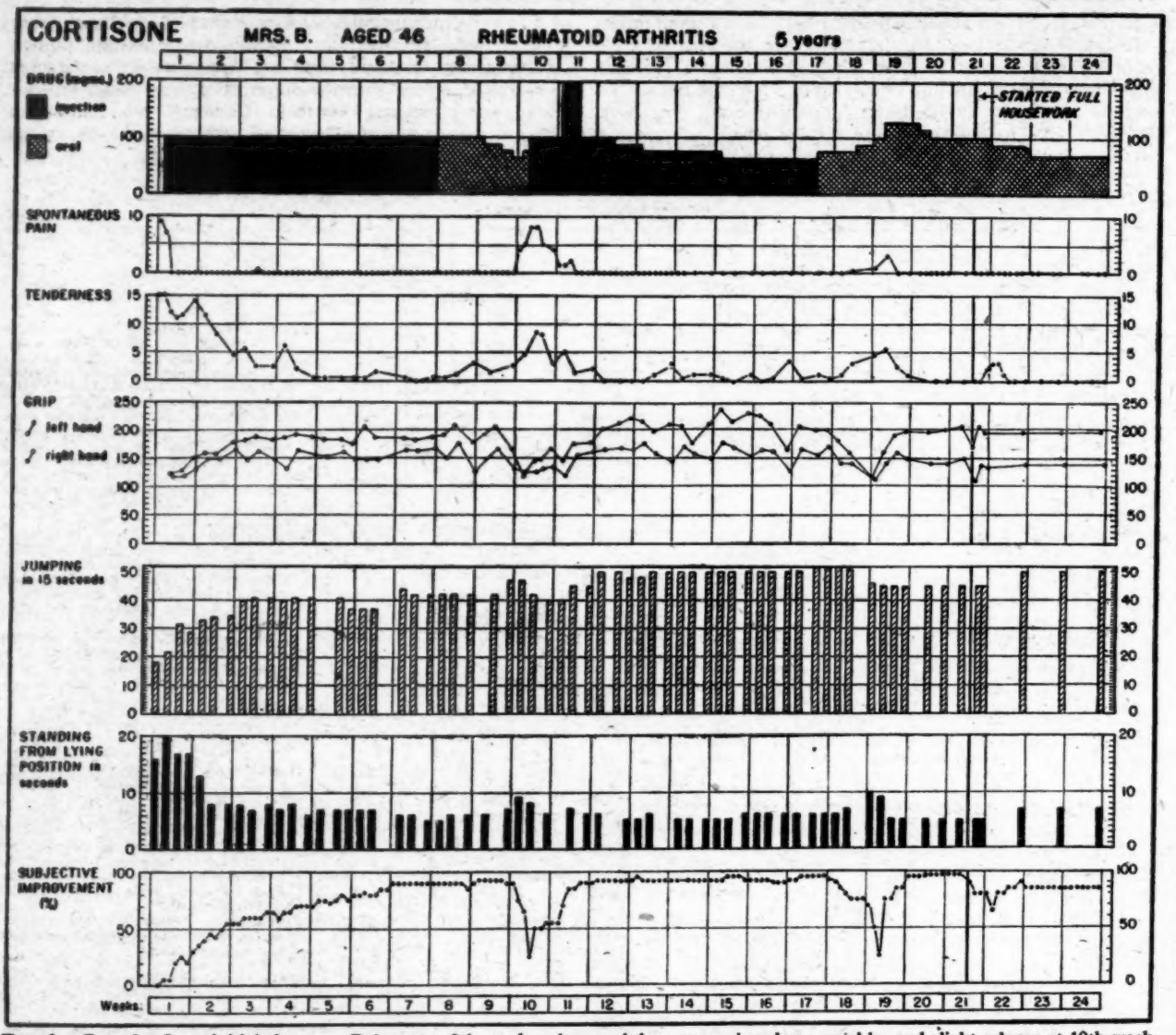

FIG. 1.—Case 5. Low initial dosage. Relapse at 9th week, when oral dose was reduced too quickly, and slight relapse at 19th week after changing to oral therapy in insufficient dosage.

Side-effects

Our series has been notable so far for the absence of serious side-effects, and in only Case 4 have they been severe enough to cause us to stop administration of the drug. Table II summarizes all the side-effects observed. In nearly every case they were slight, and might have been ignored but for the alarming reports which have been published by other observers.

Injection Abscesses.—Cortisone acetate is prepared in a microcrystalline suspension which forms a depot at the site of the injection. The injections are painless if they are placed deeply in the intramuscular tissue. An abscess may start from injection into the superficial fat, from an intramuscular haematoma, or from imperfect skin sterilization. The onset is insidious, with mild local pain but no constitutional disturbance. This failure of constitutional response can be most misleading, and in our early cases caused us to delay incision until a large amount of pus had accumulated, with considerable necrosis of the gluteal muscles. If recognized in time we have found that most of these abscesses can be satisfactorily dealt with by aspiration of the pus through a wide-bore needle and local replacement by the appropriate antibiotic.

Rounding of the Face.—This complication occurred in five cases. In two the patient was having a "boost" dose of 200 mg. a day when it appeared. In these cases it con-

TABLE II.—*Side-effects*

Case No.	No Side-effects	Injection Abscess	Rounding of Facies: Mild / Moderate / Severe	Decreased Carbohydrate Tolerance	Fluid Retention Causing Oedema	Spontaneous Bruising	Menstrual Irregularities	Paraesthesia and Enlarged Submandibular Glands	Comments	Treatment Suspended Because of Side-effects
1										
2	•	•								
3		•				•	•			
4		•	•				•			
5		•								•
6			•	•	•					
7			•		•	•		•	Oedema on high dose only	
8			•		•			•		
9	•									
10		•					•			
11		•	•							
12	•									
13	•									
14	•									
15	•									
16	•									
17							•			
18	•									
19		•								
20					•					
Total	8	7	3 mild 2 mod.	1	4	2	4	2		1

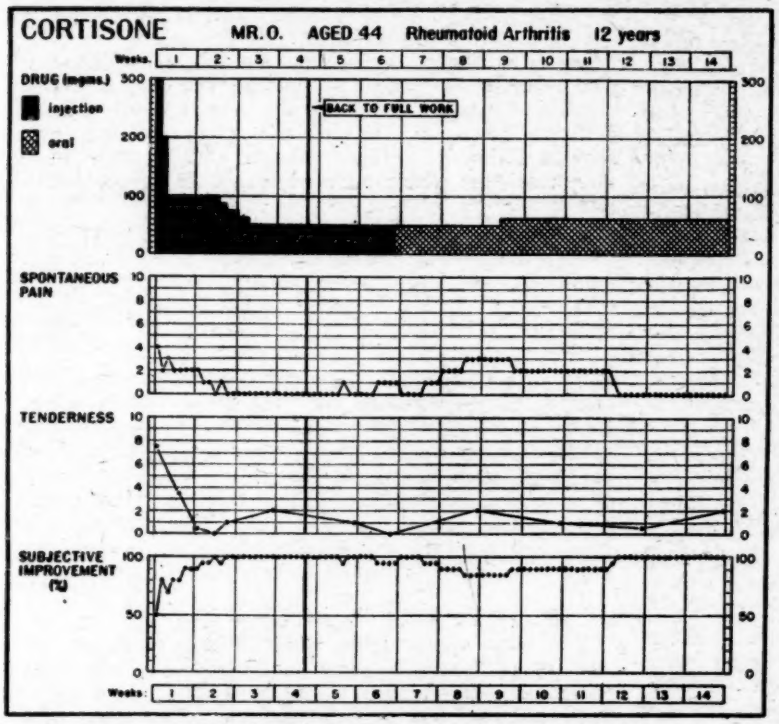

FIG. 2.—Case 9. Previous improvement with A.C.T.H. and relapsed to 50%. High initial dosage and adequate suppression of arthritis at oral maintenance dosage of 62.5 mg. a day.

sisted of a mild degree of "moon face"; there were no supraclavicular pads, no dorsal hump, no striae, and no acne, but one of the patients subsequently developed an excess of fair fine hair on her cheeks and lips. The third case (Case 6) developed a rounding of the face in association with a significant degree of water retention. Case 4 developed a "moon face," supraclavicular pads, and a small dorsal hump, but no other manifestations of Cushing's syndrome. As it was impossible to control this patient's arthritis on a lower dose and as she objected on cosmetic grounds, treatment was suspended. The nature of the "moon face" in Cushing's syndrome is not properly understood, nor is its significance in cortisone and A.C.T.H. therapy. From our brief experience with these substances it would appear that a "moon face" may occur in the absence of any other manifestation of Cushing's syndrome and is therefore merely of aesthetic concern to the patient.

Carbohydrate Tolerance.—No patient developed persistent glycosuria during treatment, but ketone bodies were occasionally found, in some cases without glycosuria. Case 6, however, had been rendered diabetic by a previous course of high-dosage A.C.T.H. therapy. (This case is to be reported in detail later.) When cortisone treatment was started he was insulin-sensitive and the diabetes was well controlled with 12 units (P.Z.I. and soluble) given once a day; but cortisone rendered him insulin-insensitive for a time, though his urine is now sugar-free on 104 units of insulin a day. It was considered justifiable to continue treatment in spite of the insulin resistance, as he was responding so well and would have become totally crippled had cortisone treatment been stopped.

Fluid Retention Causing Oedema.—Fluid retention causing temporary oedema has occurred in four cases. In Cases 7 and 8 it developed while the patient was on the "boost" dose of 200 mg. a day and soon disappeared when the dose was reduced. In Cases 6 and 20 it was controlled by moderate salt restriction in the diet.

Psychic Effects.—Possibly because our patients were chosen, among other things, for their mental stability and intelligence, we have not encountered any serious psychic effects. Some of them complained temporarily of mild exhaustion and apathy. Two complained of a feeling of tension and quick temper while on the high dosage; one complained for a short period of a feeling of unreality. There has been an absence of pathological euphoria, and in no case was insomnia a prominent symptom. Some of the patients complained of transient morning headaches, which may have been associated with mild psychological symptoms already described.

Spontaneous Bruising. — Two patients developed a mild spontaneous bruising. This is a classical feature of Cushing's syndrome. Robson and Duthie (1950), however, have observed that cortisone increases capillary resistance, in which case bruising would not be expected to occur.

Menstrual Irregularities.—The intervals between menstrual periods increased slightly in four cases without other symptoms. In Case 4 menstruation ceased after the second month of treatment, and amenorrhoea persisted until after treatment was suspended on account of the development of a "moon face," to which the patient objected on aesthetic grounds.

Oral Paraesthesia and Enlarged Submandibular Glands.—Cases 7 and 8 developed paraesthesia in their tongue and cheeks. Case 7 developed small buccal ulcers which disappeared without treatment. Case 8 has developed bilateral swelling of her submandibular glands. They are not painful, but are associated with a dryness of the mouth.

Steroid Metabolism Studies

A large number of estimations were carried out during cortisone administration. These are too voluminous to publish in detail, and the following is a summary of the main findings.

Corticoids.—The pre-treatment values of urinary formaldehydogenic steroid excretion in four cases were below the normal range for the method—namely, 0.4–1 mg./24 hours. On treatment with cortisone (100 mg./24 hours) a small increase into the normal range was observed. A further increase to levels exceeding the normal range was noted when the daily dose of cortisone was increased to 200 mg.

17-Ketosteroids.—In the seven cases studied, pre-treatment levels of 17-ketosteroid also tended to be at the lower limit of the normal range. The inception of treatment in all

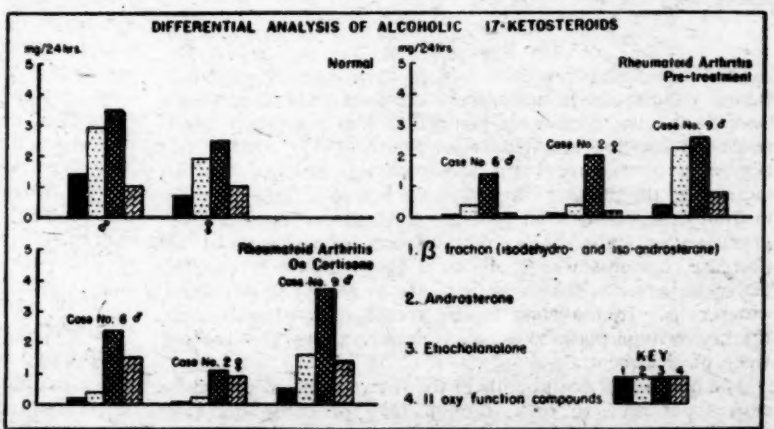

FIG. 3.—Differential analysis of alcoholic 17-ketosteroids.

cases investigated was associated with an initial fall in 17-ketosteroid excretion. On prolonged administration those cases having a relatively high pre-treatment 17-ketosteroid output continued to excrete reduced amounts, while in those cases with a low pre-treatment output excretion rose above pre-treatment levels. In the three cases in which a differential analysis of 17-ketosteroids was attempted (Fig. 3) there was an increased excretion of steroids with the 11-oxy-function—possibly catabolic products of the administered cortisone. In two of these cases, and in others not reported here, the ratio of etiocholanolone/androsterone excreted was significantly raised compared with normal subjects, although this is not necessarily of particular significance to rheumatoid arthritis (Robinson and Goulden, 1949). In no case was the raised etiocholanolone/androsterone ratio restored to normal during the treatment with cortisone; on the contrary, there was a further relative and absolute increase in etiocholanolone in two cases.

Haematological Investigations

Three cases were investigated in detail (Nos. 5, 6, and 9), including observations on all types of cell in the peripheral blood and bone marrow, and serial readings of the sedimentation rate.

Peripheral Blood

Haemoglobin and Erythrocytes.—In all three cases an increase in reticulocytes was noted during the second week of treatment, and this was followed by a rising haemoglobin and red-cell count until normal levels were reached. At the same time the cells showed a full complement of haemoglobin, and microcytosis, if it had been present, disappeared.

The Leucocytes

Eosinophils.—The administration of cortisone resulted in a diminution of 60–70% in the number of circulating eosinophils in all cases. In two cases this effect was obtained in the first 24–48 hours, but in the third case the lowest level was not reached until the fifth day. In two cases the eosinophils "escaped" to levels much above the original in two to four weeks. This phenomenon was also observed in five other patients treated with cortisone on whom eosinophil counts were performed but which were not studied in detail. In Case 9 the eosinophils returned transitorily to their original level—the marked and sustained increase noted in the other cases not being present.

Total Leucocytes.—In all cases the total count rose and a leucocytosis was observed at some stage. This contrasts with the low normal or subnormal level before treatment. The neutrophil granulocytes showed the most spectacular rise, but the lymphocytes and monocytes showed some small increases also. A lymphopenia was not observed at any stage.

Blood Platelets.—The changes in the blood platelets were not so dramatic as in the leucocytes. Generally speaking, the count appeared to follow the granulocytes—rising and falling with the level of these cells.

The Bone Marrow

The bone marrow was studied in each case by repeated sternal punctures. Initially, the bone marrow showed some increase in plasma cells—a fact which had previously been noted by Hayhoe and Robertson-Smith (1951). After the beginning of treatment the most marked change was an increase in the number of cells of the marrow. This increase in number applied to all types of cells, but particularly the granulocytes. The number of plasma cells appeared to decrease, but this was probably a relative rather than an active diminution due to an increase in the number of the other cells. In the most anaemic case (No. 6) a marked erythroid hyperplasia was also noted during the second week of treatment.

The number of eosinophils in the marrow varied considerably from time to time, though they probably decrease slightly at first but later increase.

The Plasma Volume

During treatment all patients showed some degree of fluid retention as studied by fluid-balance estimations and increase in weight. In Case 6, pitting oedema of dependent parts was noted. At the same time plasma-volume studies showed a decrease. These changes were observed in all three cases, but were most marked in Case 6, in which the results were as follows:

Date	Plasma Volume	Hb	P.C.V.
16/4/51	3·6 litres	60%—8·7	29%
27/4/51	2·0 ,,	80%—11·6	38%
8/5/51	2·0 ,,	86%—12·5	40%
12/6/51	2·2 ,,	87%—12·6	40%
21/6/51	2·4 ,,	88%—12·8	41%
13/9/51	3·5 ,,	90%—13·0	40%
29/9/51	3·5 ,,	88%—12·8	39%

It will be seen that, initially, during the period of rapid change the haemoglobin and packed-cell volume showed similar variations to the plasma volume. But, as the latter returned to its normal level rather slowly, the red cells, etc., had increased and no change was seen. The period of maximum oedema appeared to coincide with the minimum plasma volume. At the same time serum potassium levels fell from 19 mg. to 10.6 mg. per ml.—the lowest level being reached when oedema was at its height.

Effect on Serum Antibodies

The effect of cortisone administration on serum antibodies was also studied, and for this purpose the following antibodies were chosen: (1) naturally occurring alpha and beta antibodies, one or both according to the group of the case; (2) antistaphylococcal toxin titres; (3) Rose's differential agglutination titre; and (4) antistreptolysin O titre.

Among the first three groups of antibodies studied no significant change in titre was noted in any case. In two cases no change in the antistreptolysin titre was observed, but their titre was low at the beginning of treatment. In the third case (No. 6) the titre was high before treatment and the level fell from 700 units to 300 units per ml. at the end of the period of observation.

The Sedimentation Rate

Both Wintrobe and Westergren techniques were used. There did not seem to be any great difference between them, but the impression gained was that the Wintrobe was probably the more sensitive. In rheumatoid arthritis treated with cortisone, it must be emphasized that the actual level of the sedimentation rate does not appear to be of great importance, particularly in the case of the Westergren method. Thus cases which are clinically active and with numerous manifestations of the disease may have sedimentation rates only slightly above normal levels. Further, cases which are clinically progressing favourably may show a raised figure.

In this short study it was noticed that there seemed to be some correlation with the clinical condition if the general trend was noted. Thus cases which are deteriorating show a rising rate and cases improving show at first a falling rate which later flattens out and remains more or less steady, though sometimes at a figure greatly in excess of the conventional "normal." On the results so far, it would appear that the trend, rather than the absolute level, is much more significant, and if this is noted it is capable of giving some indication of the progress of the case. But the clinical assessment still remains the most important, as an intercurrent infection may raise the sedimentation rate quite independently and possibly without affecting the arthritic condition.

Discussion

It is apparent from this series of cases that the manifestations of active rheumatoid arthritis can be suppressed by the administration of cortisone. We have not encountered any case in which rheumatic symptoms are resistant to adequate doses of cortisone, and we have been impressed by the consistency of the clinical

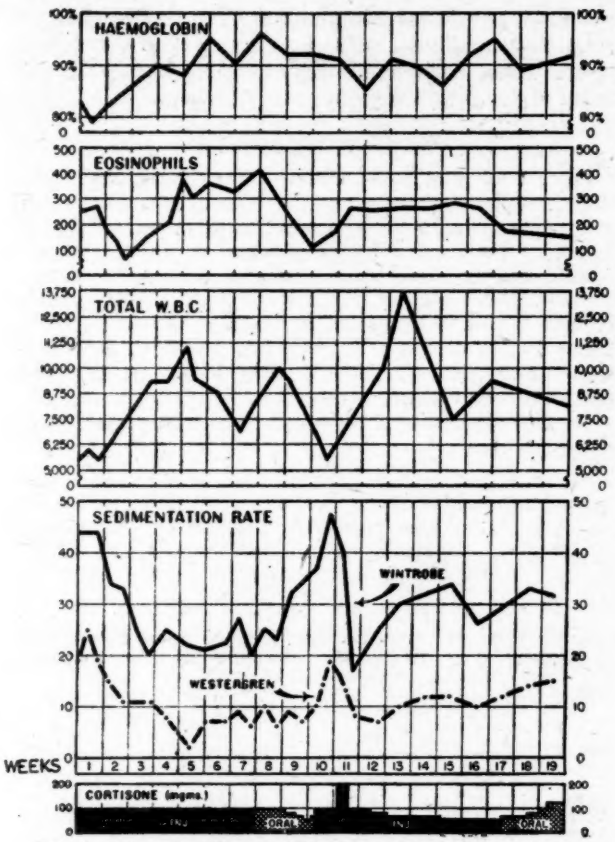

FIG. 4.—Case 5. Haematological responses with cortisone.

response as compared with the variability of the metabolic and other effects of cortisone (Browne, 1951). Where permanent damage is absent or moderate patients can eventually be returned to their own work, or to some form of lighter work, and women will be able to undertake most household duties. However, in almost every case administration has to be continued indefinitely to maintain this suppressive effect, although it seems likely that in the occasional case—for example, Case 1—cortisone can precipitate a remission of symptoms of considerable duration, and we have seen and heard of other such cases.

The success of cortisone treatment depends upon careful selection of cases and is much influenced by the difference between the suppressive dose and the "toxic" dose. This varies greatly from patient to patient and cannot be predicted in any given case.

Where the margin is large, as for example in Case 3, cortisone administration is both simple and highly satisfactory; where it is small (Case 4) it may be extremely difficult to achieve and maintain the balance between the control of symptoms and the incidence of undesirable side-effects.

Nevertheless we are of the opinion that there is a tendency at the moment to attach too great significance to mild side-effects, such as facial rounding and slight irregularity of the menstrual cycle. For instance, the incidence of side-effects reported by Ward *et al.* (1951) was 63% of 21 cases treated by 75 mg. or more of oral cortisone daily, though all these side-effects were reversible and none necessitated the discontinuance of treatment. The preoccupation of many observers with these mild side-effects reminds one of a house-proud woman overconscious of a speck of dust which the visitor has not noticed.

It would appear from our series that no single-cell type of blood investigation is of much value as a method of controlling treatment. Indeed, the changes observed in the blood all appear to be secondary to the general effect of the drug on the body as a whole—the changes in the blood being indirect. Apart from the first few days of treatment, eosinophil counts are unreliable and their level would seem to have little or no bearing on the clinical progress of the case. The remaining blood changes, if viewed as a whole, may, however, give some indication. The sedimentation rate is of some help, but even here it is the general trend rather than the absolute level which must be noted. Any sustained or sharp increase heralds deterioration in the clinical condition. Any marked and sustained fall in the erythrocyte, leucocyte, or haemoglobin levels, particularly that of the granulocytes, coincides or precedes a clinical deterioration, but the correlation is not absolute and is in the nature of a pointer—a danger signal. The clinical assessment still remains the best and most reliable guide to progress.

The discovery of this form of treatment emphasizes the importance of the early diagnosis of rheumatoid arthritis. It is probable that the results achieved in our series, in which we purposely excluded very early cases, could have been further improved—on a lower dosage and therefore with fewer side-effects—if earlier cases without joint damage had been selected. Cortisone will have little effect where extensive joint damage is present, and may be dangerous in view of the high dosage required to obtain a small amelioration of symptoms.

Until the significance of cortisone's side-effects is more fully understood, our aim should be to maintain the patient in a state in which he remains reasonably comfortable. We do not consider it advisable to attempt to suppress the symptoms of rheumatoid arthritis completely when this requires a high maintenance dosage.

Summary

Twenty selected cases of active rheumatoid arthritis have been studied during prolonged cortisone administration and have been separately assessed from the clinical, haematological, and metabolic aspects.

In 17 cases the patient has been enabled to return to previous work or household duties.

In only one case has it been possible to stop administration.

Certain methods of dosage have been assessed and side-effects have been studied.

The cortisone used in this study was provided from a generous gift made jointly to the Medical Research Council and the Nuffield Research Foundation by Messrs. Merck & Co., Inc. We wish to acknowledge the valuable assistance given to us by Dr. B. Gottlieb, consultant physician, St. Mary Abbots Hospital, and his assistants, and by the following pathologists and biochemists and their assistants: Dr. H. E. Archer and Dr. R. G. L. Waller, West London Hospital, and Dr. A. G. Signy, St. Mary Abbots Hospital.

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SICKLE-CELL TRAIT IN SOUTHERN INDIA

BY

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When the traveller in East and Central Africa inquires from the inhabitants about their distant past, they will often tell him of tall men, fairer than themselves, bearded and with long hair, who came from afar bringing codes of law, handicrafts, and cattle.

Several leading anthropologists have speculated whether there were migrations to prehistoric Africa from other continents, possibly Asia. Such speculations have been supported by the observation that the tall, broad-shouldered skeleton of the modern Bantu appears only in Neolithic excavations, whereas the types found in older strata are more slender. It had been noted that, with the exception of the Ankole herds, which are related to those of ancient Egypt, the East African cattle show a resemblance to the Indian cow. Similarities are also found between the poultry of Africa and India.

Fortunately for anthropologists the present-day inhabitants of Africa possess distinctive features in their blood—the sickle-cell trait, a very high incidence of a particular combination of Rh antigens known as R_o (cDe), and another blood-group antigen provisionally referred to as He. So far as we know, the sickle-cell trait and sickle-cell anaemia have not been reported in people who were not either Africans or members of groups which must be expected to have an admixture of African blood. For example, Negro slaves undoubtedly mixed with Mediterranean races in Roman times. The sickle-cell trait has not been found in races which do not also show a raised incidence of the gene combination R_o (cDe) (Mourant, 1951). This combination is found comparatively rarely in Northern and Central Europe and in Northern India, with a frequency of approximately 2%. By contrast, it has a frequency of over 50% in all African populations south of the Sahara so far tested. It is distributed fairly evenly all over tropical Africa, regardless of the incidence of the sickle-cell trait (Wiener, 1946; Boyd, 1950; Ikin and Mourant, 1952). The antigen here called He has been detected in about 5% of West Africans but has not been found in the course of testing about 1,000 Europeans (Ikin and Mourant, 1951, 1952).

It seemed possible that an investigation of the blood of certain Southern Indian communities might serve to refute or support the idea of a racial link between Africa and India. The aboriginal tribes were chosen as the group in whom a search for African blood features appeared most likely to yield positive results.

There is no general agreement how the peoples of South India should be classified. They have in the past often been divided into settled communities, or Dravidians, and aborigines, or Pre-Dravidians, but there are objections to this on both linguistic and cultural grounds; nor does the division correspond clearly to anything in the history of these populations. The so-called Pre-Dravidians of the Nilgiri Hills vary from civilized agricultural communities such as the Badagas (who have affiliations with the Canarese) to tribes such as the Irulas, Kurumbas, and Paniyans, who are found living under primitive conditions in the jungle.

Materials and Methods

Three aboriginal communities—the Badagas, the Todas, and the Irulas—were investigated. Sex, approximate age, and relationship to other persons tested were noted. To determine the incidence of the sickle-cell trait each blood sample was examined after incubation with a 2% sodium metabisulphite solution (Daland and Castle, 1948). Blood samples were collected from 60 Todas, 60 Badagas, and 80 Irulas for the determination of blood groups in the following systems: ABO, MNS, Rh, Duffy, P, and for the detection of the He antigen.

A control group of other peoples was investigated for the sickle-cell trait.

Results

The sickle-cell-trait incidence among 191 unrelated Badagas was 8.4%, among 60 Todas 3.3%, and among 80 unrelated Irulas 30%. No sickle-cell trait was found among 443 unrelated members of other communities of the region (see Table).

The Incidence of the Sickle-cell Trait in Some South Indian Communities (With the exception of the Todas, all individuals are unrelated)

Population	Number Examined	Sickle-cell Trait	
		Number of Individuals	%
Irulas	80	24	30
Badagas	191	16	8·4
Todas	60	2	3·3
Tamils	128	0	0
Malayalis ..	111	0	0
Canarese	95	0	0
Telegus	109	0	0

All first-degree relations have been excluded from the Table, except in the case of the Todas. As the whole Toda community numbers fewer than 500 individuals, practising polyandry, it was impossible to exclude close relatives. However, the 60 samples were collected from seven widely separated settlements; the two sickle-cell-trait carriers were children living in settlements some miles apart.

The incidence of the Rhesus chromosome R_0 (cDe) was at the low level found in Europeans and Northern Indians, rather than at that found in Africans. Among 60 Badagas, 2 individuals were of the phenotype R_0 or ccDee; among 60 Todas, 2; and among 80 Irulas, none.

None of the 120 blood samples contained the He antigen.

Discussion

These findings lend support to the idea of an Indian migration to Africa in prehistoric times. The reverse possibility—an influx of African blood bringing the sickle-cell trait to the hills of Southern India—should have resulted in a raised incidence of the gene combination R_0 (cDe). The fact that the incidence of R_0 is high everywhere among the negro races of Africa, whereas the incidence of the sickle-cell trait shows wide variations among them, suggests that Africa received the sickle-cell trait at a period too recent to allow an even distribution over the continent. It is realized that there are other possible interpretations of the above results.

It is not suggested that the actual migrants to Africa were Badagas or Todas or even Irulas. The first came from the North to the Nilgiri Hills only within the last 1,000 years; the second, though allegedly autochthonous, resemble Europeans in appearance and in their possession of the subgroup A_2 and of the Rh genotype rr (cde/cde). It is likely that at least the Badagas and Todas received the sickle-cell trait from older Southern Indian communities.

The examination of "pre-Dravidian" people is being continued with the hope of further defining the distribution of the sickle-cell trait in Southern India. However, the main purpose of the investigation has been achieved since the results lend support to the possibility of a link between prehistoric Africa and India.

Summary

The sickle-cell trait was found to be present in a number of individuals belonging to three aboriginal communities of Southern India. There was a low incidence of the Rh chromosome R_0 (cDe).

No sickle-cell-trait carrier was discovered among a control group of the non-aboriginal or "Dravidian" population.

The possible anthropological significance of these findings is discussed.

We should like to thank the Minister of Health of the Government of India and the Secretary of the Indian Council of Medical Research for making the necessary arrangements for these investigations. We are especially indebted to Dr. V. N. Patwardhan, Director of the Nutrition Research Laboratories, Coonoor, and to Dr. N. Veeraraghavan, Director of the Pasteur Institute, Coonoor, for generously allowing us laboratory facilities. We also wish to thank Dr. A. E. Mourant, of the Blood Group Reference Laboratory, London, for supplies of testing sera. The expenses of this work were generously defrayed by the Nuffield Foundation.

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THE SICKLE-CELL TRAIT IN WESTERN NIGERIA

A SURVEY OF 1,881 CASES IN THE YORUBA

BY

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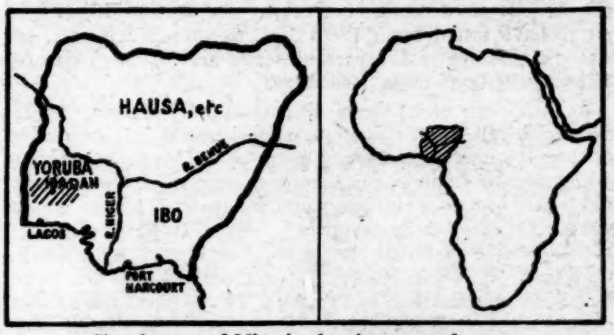
Yorubaland occupies the greater portion of Western Nigeria, lying between the Lagos lagoon in the south, the River Niger in the north, the Dahomey frontier in the west, and the Benin country in the east. Ibadan itself is a huge sprawling city of mud-brick buildings. The population, which is mainly Yoruba, is in the region of half a million. Ibadan's present importance is due to the fact that it lies at the centre of the cocoa-growing area of Nigeria, although it has been the site of a considerable town for over a hundred years.

The Yoruba are for the most part peasant farmers and petty traders. Their diet is largely vegetarian, the staple farinaceous foods being yams, maize, and cassava. Animal protein is deficient in the food of the majority, as cattle cannot be reared locally but have to be brought for slaughtering from northern Nigeria.

Groups Examined

In this survey 1,881 Yoruba were examined. The majority were from Ibadan, although some came from all parts of Yorubaland. Sickling was looked for by the method of Scriver and Waugh (1930), although no preliminary congestion was used. The finger was pricked and a drop of blood transferred to a coverslip. This was inverted and placed face downwards on a clean slide. The coverslip was ringed with petroleum jelly and the preparation examined for sickling after 72 hours. In a few, the enclosed blood became either haemolysed or dried. These cases were not included in the series.



Sketch map of Nigeria showing area of survey

It is felt that the cases reviewed here represent a fair cross-section of the Yoruba population of Ibadan. The newborn babies were examined in the maternity wards and the other infants while attending welfare clinics. The older pre-school children and the elderly were difficult to test in large numbers. The few that were examined were in-patients, out-patients, or visitors at hospital. The three groups of schoolchildren were tested at several schools serving a wide area of the town. The young adult male group was the least balanced, as the majority were either policemen or Army recruits, and were probably of more than average physical development.

Results of the Survey

The results are shown in Table I. The average incidence in the whole series of 1,881 was 23.7%. As can be seen, no case of sickling was observed in any of the 51 newborn babies examined. The possible significance of this is discussed later. In the other groups the incidence of sicklaemia varied from 19.2% in young adult males to 28.3% in children between the ages of 1 and 4 years. If the first group containing babies up to 2 weeks old is omitted from analysis, a χ^2 test shows that the proportions of positive cases in the other age groups do not vary more than would be expected by chance ($\chi^2=8.83$). For 7 degrees of freedom P lies between 0.3 and 0.2. In other words, the sickle-cell trait would appear to occur with equal frequency at all ages, with the exception of the newborn.

TABLE I.—*Results of Survey for the Sickle-cell Trait in 1,881 Yoruba*

Age	No. Examined	No. Positive	% Positive
1st 2 weeks	51	None	—
Over 2 weeks to 1 year	120	30	25·0
„ 1 year to 4 years	60	17	28·3
„ 4 years „ 8 „	301	84	27·9
„ 8 „ „15 „	512	133	25·0
„ 15 „ „18 „	144	30	20·9
Young adult males	302	58	19·2
„ females	339	80	23·6
Older adults (males and females)	52	14	26·9
Total	1,881	446	23·7

Discussion

Comparatively few surveys for the sickle-cell trait have been undertaken in tropical Africa, and results in different countries vary. Thus, 45% of the pygmoid Baamba show sickling (Lehmann and Raper, 1949), while Sarmento (1944) found only 8% positive in a survey of adult males in

Angola. It is, however, correct to say that most investigators have found from 15 to 30% to show sicklaemia, so that the findings in the present series are in rough accord with observations made elsewhere.

As has been stressed by several authors (Raper, 1950), the sickle-cell trait is common in tropical Africa, while sickle-cell anaemia is rarely recorded. This is in contradistinction to findings in American negroes, in whom the sickle-cell trait is much less common (6–9%), but in whom sickle-cell anaemia is frequently seen. It has been estimated that in America the ratio of sickle-cell anaemia to trait is 1:50, while Raper (1950) estimates that the ratio in Africa must be below 1:1,000. The explanation of this undoubted fact is unknown. Raper suggests that it may be connected with genetic modification produced by intermarriage with Caucasians in the case of the American negro. However, as has been pointed out elsewhere (Jelliffe, 1952), it must be realized that a partial explanation for the rare reports of sickle-cell anaemia in Africa lies in the comparatively few doctors and laboratories in these regions, together with a lack of awareness of the disease entity and the difficulty of making a rapid and certain diagnosis, especially in view of the numerous other forms of anaemia which occur so commonly in indigenous Africans. The possibility that sickle-cell anaemia may be more frequent than has hitherto been suspected is suggested by Jelliffe and by a recent report from Kenya (Foy, Kondi, and Brass, 1951).

At the present state of knowledge, it nevertheless seems certain that sickle-cell anaemia is relatively rare in tropical Africa, despite the presence of an enormous population showing the sickle-cell trait. This is confirmed by the present survey. Of the 1,881 cases examined, none were observed to have an obvious haemolytic anaemia, although this cannot be regarded as scientific evidence, as neither careful clinical examinations nor full haematological investigations were undertaken. However, it is significant that, during the past nine months in Ibadan, where there must be over 100,000 persons with the sickle-cell trait, only 12 cases of sickle-cell anaemia have been seen.

The mode of inheritance of sickle-cell anaemia and its relation to the sickle-cell trait is still far from certain. The most recent suggestion (Neel, 1949) is that sickle-cell disease may be due to a gene which in a homozygous condition produces sickle-cell anaemia and in the heterozygous condition sicklaemia (sickle-cell trait). As Lehmann (1951) has noted, if this theory is correct, sickle-cell anaemia would be expected to occur more frequently in Africa than in America. As he remarks, "One possible explanation for this discrepancy could be that the gene is lethal and that homozygotes die earlier than the rest of the population." If this were the case the incidence of sickling would be expected to fall in the older age groups, whereas the frequency was found to be the same at all ages in three tribes examined in Uganda.

As has been noted previously, in the present series no variation in incidence could be found in the different age groups, with the exception of the newborn babies. This can be interpreted as supporting Lehmann's view that the simple homozygous-heterozygous theory does not appear to fit the facts as seen in tropical Africa. The most interesting feature of this survey was the apparent absence of sickling in newborn children examined in the first two weeks of life. In no instance were sickle-cells seen after 72 hours' observation; and, in order to follow up this type of case more carefully, blood from the last 18 newborn babies was examined again after 216 hours. The results are recorded in Table II. As can be seen, 12 showed no sickling even after this interval, 5 specimens were haemolysed, while 1 case showed the presence of less than 5% sickle cells.

It has recently been shown that the haemoglobin of sickle-cell anaemia and normal haemoglobin differ physicochemically, and that the haemoglobin of a subject with the sickle-cell trait is a mixture of the two (Pauling *et al.*, 1949). A possible explanation for the absence of sickling in these newborn infants is that sickle-cell haemoglobin is not present

TABLE II.—*The Sickle-cell Trait in the Newborn*

Case No.	Age in Days	Result at 72 Hours	Result at 216 Hours
1	5	Negative	Negative
2	8	"	"
3	7	"	"
4	2	"	Haemolysed
5	4	"	"
6	10	"	Negative
7	3	"	"
8	5	"	"
9	3	"	"
10	4	"	Haemolysed
11	6	"	Under 5% positive
12	3	"	Negative
13	1	"	Haemolysed
14	5	"	"
15	7	"	Negative
16	4	"	"
17	4	"	"
18	6	"	"

in foetal blood but develops after birth. Unfortunately, it was not possible to follow up this series of cases. In addition, in the normal subject, foetal haemoglobin has different biophysical properties from adult haemoglobin, although exact differences in chemical structure are still far from clear-cut. However, it is well recognized that foetal haemoglobin has an increased affinity for oxygen and that, conversely, it reduces more slowly. It has been shown by various workers that foetal haemoglobin persists, to a diminishing degree, in the blood of newborn infants, although the length of time it can be detected is uncertain. Periods varying from days to a few months have been described by different investigators (Smith, 1945).

Sickling of red blood corpuscles probably occurs only when haemoglobin is in a reduced state, at least in subjects showing the sickle-cell trait. It seems possible, therefore, that the apparent absence of sickling in the first two weeks of extrauterine life may be due to this persistence of foetal haemoglobin, and that sickling cannot be demonstrated because of the extreme difficulty of causing this type of haemoglobin to become reduced.

In this context it may be mentioned that recent work by Liquori (1951) has shown that in Cooley's anaemia, a disease with many points of similarity to sickle-cell anaemia, 40–60% of the haemoglobin may still be foetal at the age of 8 years. Although this is in contrast to the hypothesis suggested here, nevertheless both findings would seem to indicate that further work on the relation of foetal haemoglobin to sickle-cell haemoglobin is required.

Summary

A survey for the sickle-cell trait was undertaken in 1,881 Yoruba in Ibadan, Western Nigeria. The average incidence was 23.7%. The incidence showed no real variation with age, although no cases of sickling were noted in 51 newborn babies. The latter was thought to be related to a persistence of foetal haemoglobin into the first weeks of extrauterine life. The results of the survey are discussed, with especial reference to the homozygous-heterozygous theory of inheritance of the sickle-cell trait.

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IRON AND THE "PHYSIOLOGICAL" ANAEMIA OF PREGNANCY*

BY

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AND

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The volume of the vascular bed increases during pregnancy, necessitating a commensurate increase in the blood volume. Dieckmann and Wegner (1934) found that the total blood volume was increased by 23% during pregnancy, and that, although this increase was proportionately much greater in the plasma content, the cellular element was also increased. Since the haemoglobin level tends to return to normal values during the puerperium there would appear at first sight to be a prima facie case for the assumption that the anaemia of pregnancy is physiological and for the acceptance of the minimal normal figures of: haemoglobin 10 g.%, erythrocytes 3,360,000, and a packed cell volume of 33%, which were suggested by Adair, Dieckmann, and Grant (1936). On the other hand, many investigators deny that haemodilution can cause such low figures as those quoted above, and believe that the so-called physiological anaemia of pregnancy denotes a marked deficiency of iron.

Before animadverting upon the conflicting reports in the literature it is desirable to see the main factors of the problem in perspective. They are: the level of the maternal haemoglobin before pregnancy occurs, the cessation of menstruation during pregnancy, the increased blood volume, and the foetal demand for iron.

Davies *et al.* (1946), in a survey of 2,000 women in the London region, found that anaemia was encountered twice as often in married as in single women, and there is evidence, particularly that emanating from the blood transfusion services, that anaemia is more widespread in England in 1951 than it was in 1946. Strauss and Castle (1932), Strauss (1934), Corrigan and Strauss (1936), Linder and Massey (1939), Young *et al.* (1946), Laurell (1947), Cartwright and Wintrobe (1949), Lundström (1950), and Ventura and Klopper (1951) are all of the opinion that there is manifested during pregnancy a tendency towards anaemia which is commonly caused by iron deficiency. Davidson and Fullerton (1938) showed that the saving of iron due to the cessation of menstruation failed to counterbalance the loss of iron to the growing foetus, and maintained that the normal pregnant woman is dangerously near to iron starvation. Whitby and Britton (1942) assert that an erythrocyte count below four millions is pathological, and Vaughan (1936) doubts whether an anaemia which responds to iron can be physiological.

On the other hand, Wolff and Limarzi (1945) regard a normocytic normochromic anaemia occurring during pregnancy as physiological and, together with Rath and Finch (1949), consider it unnecessary to give iron to pregnant women unless there is evidence of pathological anaemia. Some observers, indeed, regard the lowered blood viscosity associated with the hydraemia of pregnancy as mechanically advantageous, and it is true that the loss of haemoglobin during delivery is thereby lessened.

Adair *et al.* (1936) and Evans (1943) go further and aver that iron administered during pregnancy fails to maintain the normal level of haemoglobin. Dieckmann *et al.* (1950) have more recently shown that the addition of molybdenum renders the iron more efficacious, and in an earlier paper Dieckmann *et al.* (1949) showed that even in cases of true anaemia of pregnancy the haemoglobin can be raised from 9.9 to 11.8 g.% by this modified form of iron therapy.

The Present Investigation

This clinic serves a large industrial area in the centre of the heavy woollen industry. The purpose of the investigation was to report: (1) the incidence of anaemia in patients attending the antenatal clinic; (2) the results obtained by administering iron from the 16th week of pregnancy until term; (3) the results obtained by administering iron for eight weeks only, beginning at the 24th week of pregnancy; and (4) whether the addition of a small amount of molybdenum increases either the absorption or the utilization of iron.

All the patients who participated in the following investigations were in the third decade of life, and each group was carefully matched according to age, parity, previous health, and home conditions. They were all reasonably healthy, and each case was carefully supervised by one of us (N. B.), who got to know each woman personally.

All these women took four tabellae calcii cum vitamino D (*N.F.*) daily. Each tablet contained calcium sodium lactate, 7½ gr. (488 mg.), calcium phosphate, 2½ gr. (163 mg.), and calciferol 1/4.800 gr. (0.014 mg.), which is equivalent to 500 international units of vitamin D. They also took the extra rations and vitamins supplied by the Ministry of Food.

Experiment 1.—Seventy-two patients at or before the 16th week of pregnancy whose initial haemoglobin levels were not below 11 g.% were divided into two matched groups—A and B, the latter being the control group. *Group A* took iron in the form of tabellae ferri sulphatis compositae (*N.F.*), two tablets thrice daily. Each tablet contained: exsiccated ferrous sulphate, 3 gr. (195 mg.), copper sulphate, 1/25 gr. (2.4 mg.), and manganese sulphate, 1/25 gr. (2.4 mg.). *Group B (Control)* took a mixture known as "mist. antenatal," which was made up to the following prescription:

Syrup	20 min. (1.2 ml.)
Glycerin	10 min. (0.6 ml.)
Blackcurrant flavouring q.s.	
Aqua	to 1 fl. dr. (3.5 ml.)

1 fl. dr. (3.5 ml.) to be taken twice daily.

Experiment 2.—Thirty patients at or before the 16th week of pregnancy whose initial haemoglobin levels were not below 11 g.% were divided into two matched groups C and D. *Group C* took tabellae ferri sulphatis compositae (*N.F.*), two tablets thrice daily for eight weeks, beginning at the 24th week of pregnancy. *Group D* took White's "mol-iron" tablets,* two thrice daily for eight weeks, beginning at the 24th week of pregnancy. Each tablet contained ferrous sulphate, 3 gr. (195 mg.), and molybdenum oxide, 1/20 gr. (3 mg.).

Methods of Blood Examination

Investigations were carried out at monthly intervals until term, and again on the sixth day of the puerperium. The estimations made were the haemoglobin and the packed cell volume, from which was calculated the mean corpuscular

*The expenses of this investigation were defrayed by a grant from the Endowment Fund generously afforded to one of us (G. W. T.) by the Bradford Hospital Management Committee (A), to whom we express our grateful thanks.

*These tablets, similar to those used by Dieckmann *et al.*, were most generously sent to one of us (G. W. T.) free of all cost through the kindness of Dr. H. A. Strade, of the Medical Department of Messrs. White Laboratories, Inc., Newark, New Jersey.

haemoglobin concentration. The haemoglobin was estimated by means of a Sahli colorimeter (standard 14.8 g. = 100%). This was calibrated at the beginning of the experiment and recalibrated six months later. The packed cell volume was estimated by Wintrobe's method.

The initial haemoglobin estimations used in Fig. 1 were made by the pathological laboratory of St. Luke's Hospital, and were estimated by means of a "unicam" photoelectric colorimeter. The remaining blood examinations were carried out by one of us (N. B.) not more than 30 minutes after collecting the blood.

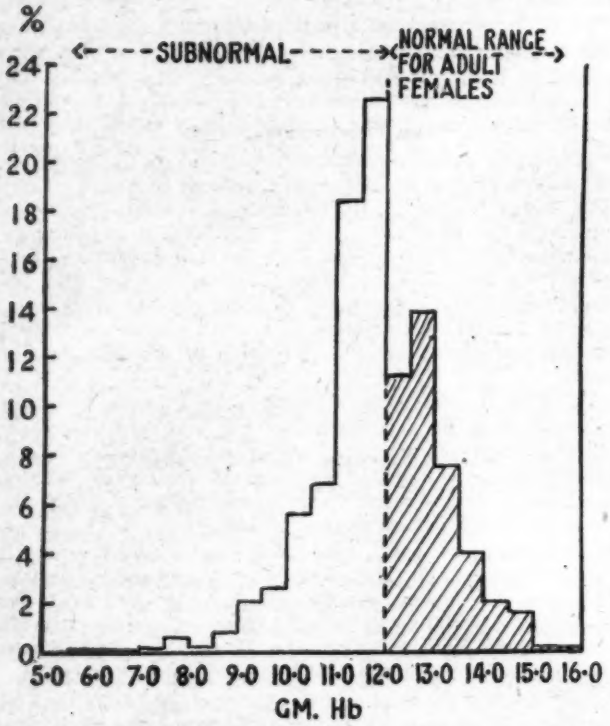

FIG. 1.—Distribution of the initial haemoglobin values of the 2,000 consecutive antenatal patients mentioned in the text.

The initial haemoglobin estimations of 2,000 consecutive cases, all less than 16 weeks pregnant, attending the booking-in clinics from January to October, 1950, were as follows (see Fig. 1):

40.15%	had readings of			12 g.	or more	per	100	ml.
59.85%	"	"	"	below 12 g.		"	"	"
37.25%	"	"	"	"	11.5 g.	"	"	"
18.85%	"	"	"	"	11 g.	"	"	"
12.05%	"	"	"	"	10.5 g.	"	"	"
6.55%	"	"	"	"	10 g.	"	"	"

Notes on Statistical Analysis of Experiments.—The standard error of the difference between the means was calculated by using the second method described by Bradford Hill (1948), and, in order to facilitate these calculations, the haemoglobin estimations are all reported as percentages. Where the difference between the means (D.M.) is greater than twice the standard error of the difference between the means—that is, D.M./S.E.D.M.>2—it is regarded as significant.

Discussion of Results

It is a matter of no little concern that 6.5% of 2,000 consecutive patients attending this clinic were severely anaemic at the 16th week of pregnancy, before any significant haemodilution had occurred, and that about 60% of all cases showed readings below 12 g.%. The normal range for adult non-pregnant women is regarded by Whitby and Britton as lying between 12 and 15.5 g.%.

The results reported in Figs. 2 and 3 and in Tables I to III vary significantly from those published by most other

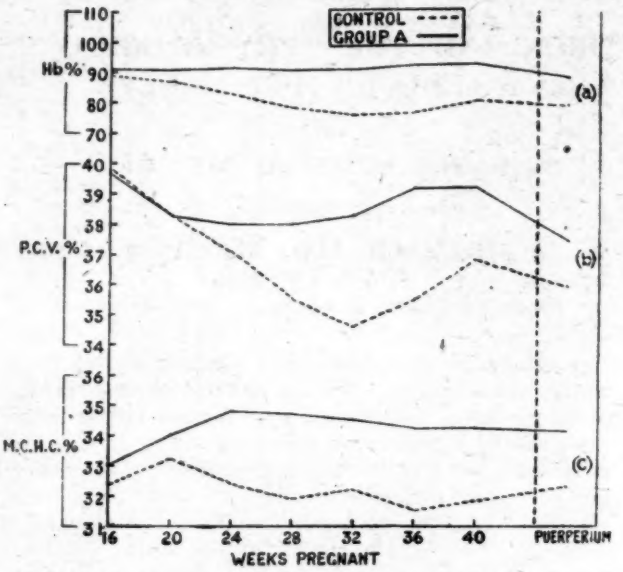

FIG. 2.—Experiment 1. (*a*) Shows the arithmetic means of the haemoglobin values plotted at four-weekly intervals in group A and the control group B. (*b*) Shows the arithmetic means of the packed cell volume in the same two groups plotted at the same intervals of time. (*c*) The curves denote the arithmetic means of the mean corpuscular haemoglobin concentration of groups A and B at the same time intervals.

authors. It will be seen that the adequate administration of iron makes it possible for normal haemoglobin values to be maintained throughout pregnancy, whereas if the woman does not take iron she begins the puerperium with a significantly lessened amount of haemoglobin.

This latter observation is all the more important when it is realized that the average initial haemoglobin value for the control group (B) was 88.8%, which means that the subjects chosen for the investigation were almost exclusively recruited from 40% of those who booked at the clinic (see Fig. 1).

Similar advantages are observed in the mean corpuscular haemoglobin concentrations from taking iron throughout pregnancy, but although the differences between the two

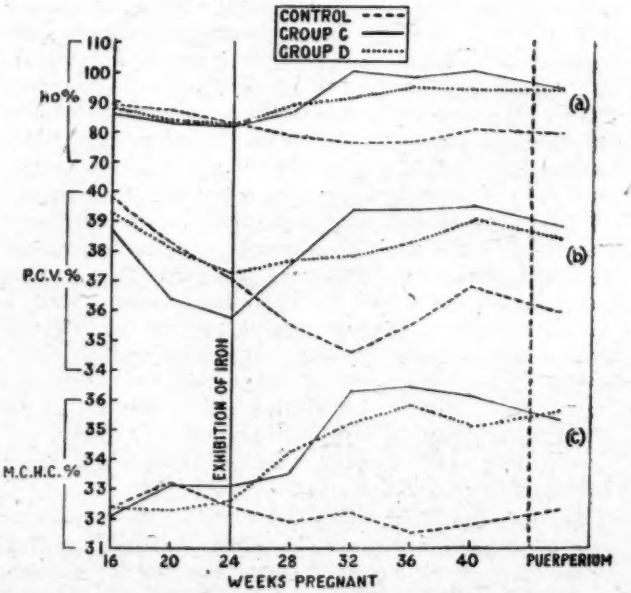

FIG. 3.—Experiment 2. (*a*) Shows the arithmetic means of the haemoglobin values for groups B (control), C, and D plotted at four-weekly intervals. (*b*) The curves denote the arithmetic means of the packed cell volumes in the same three groups plotted at the same time intervals. (*c*) The curves show the arithmetic means of the mean corpuscular haemoglobin concentration of the same three groups at identical intervals of time.

groups on the sixth day of the puerperium are significant, it will be noted that the value for the 16th week of pregnancy in the control group is almost identical with that for the sixth day of the puerperium.

It is certainly a matter of interest that the administration of iron for eight weeks only, beginning at the 24th week of pregnancy, causes a rapid recovery from the commencing "physiological" anaemia, and that thereafter satisfactory normal blood values are maintained. It will be observed that all the figures for the sixth day of the puerperium are higher in groups C and D than in Group A.

This investigation provides no evidence to support the contention of Neary (1946), Chesley and Annitto (1948), and Dieckmann *et al.* (1949), that molybdenized iron is more efficacious than ferrous sulphate in either the treatment or the prevention of anaemia during pregnancy. On the other hand, the important observation made by both Neary (1946) and Chesley and Annitto (1948) that molybdenized iron is more easily tolerated has been amply confirmed. It was found that 33% of the patients in group A and 40.2% in group C found it difficult or impossible to tolerate ferrous sulphate tablets, and it can be assumed that between 30 and 40% of all antenatal patients will not, in fact, take these tablets if they are routinely prescribed in the antenatal department. The mol-iron tablets were tolerated by 86% of the patients in group D and were equally well tolerated by other patients not included in the experiment (Table IV). It must, however, be borne in mind that the old scale preparation

TABLE I.—*Experiment 1 (Groups A and B) (See Fig. 2)*

	Weeks Pregnant							Puerperium
	16	20	24	28	32	36	40	
Average Hb estimations (%):								
Group A	90·8	90·6	91·5	90·7	91·2	92·9	93·3	88
Control (group B)	88·8	87·4	83·2	78·7	76·6	77·1	80·8	79·5
S.E.D.M.	2·67	2·38	2·16	2·23	1·75	2·18	3·63	2·83
Significance (D.M./S.E.D.M. >2) ..	0·75	1·35	3·05	5·38	8·35	7·25	3·44	3·26
Average P.C.V. (%):								
Group A	39·7	38·3	38	38	38·3	39·2	39·2	37·4
Control (group B)	39·8	38·3	37·1	35·5	34·6	35·5	36·8	35·9
S.E.D.M.	0·88	0·85	0·64	0·597	0·54	0·614	0·965	1·01
Significance (D.M./S.E.D.M. >2) ..	0·114	0	1·4	4·9	6·81	6·03	2·7	1·49
Average M.C.H.C. (%):								
Group A	33·0	34·0	34·8	34·7	34·5	34·2	34·2	34·1
Control (group B)	32·4	33·2	32·4	31·9	32·2	31·5	31·8	32·8
S.E.D.M.	0·815	0·66	0·61	0·409	0·588	0·673	1·02	0·721
Significance (D.M./S.E.D.M. >2) ..	0·736	1·21	3·91	6·85	3·91	4·01	2·35	2·5

TABLE II.—*Experiment 2 (Groups B and C) (See Fig. 3)*

	Weeks Pregnant							Puerperium
	16	20	24	28	32	36	40	
Average Hb estimations (%):								
Group C	85·8	83·3	82·3	86·7	100·6	98·2	100·1	94·3
Control (group B)	88·8	87·4	83·2	78·7	76·6	77·1	80·8	79·5
S.E.D.M.	3·19	2·42	3·44	2·92	2·83	3·55	3·57	3·4
Significance (D.M./S.E.D.M. >2) ..	0·94	1·69	0·262	2·74	8·48	5·94	5·41	4·35
Average P.C.V. (%):								
Group C	38·7	36·4	35·8	37·6	39·4	39·4	39·5	38·8
Control (group B)	39·8	38·3	37·1	35·5	34·6	35·5	36·8	35·9
S.E.D.M.	0·945	1·3	1·06	0·834	0·725	0·729	1·11	1·18
Significance (D.M./S.E.D.M. >2) ..	1·16	1·46	1·23	2·52	6·62	5·35	2·43	2·46
Average M.C.H.C. (%):								
Group C	32·1	33·1	33·2	33·5	36·3	36·4	36·1	35·3
Control (group B)	32·4	33·2	32·4	31·9	32·2	31·5	31·8	32·3
S.E.D.M.	1·02	1·19	1·11	0·822	0·757	0·791	1·18	0·802
Significance (D.M./S.E.D.M. >2) ..	0·294	0·084	0·721	1·95	5·42	6·19	3·64	3·74

TABLE III.—*Experiment 2 (Groups B and D) (See Fig. 3)*

	Weeks Pregnant							Puerperium
	16	20	24	28	32	36	40	
Average Hb estimations (%)								
Group D	88·0	83·8	83·7	89·4	91·7	95·2	94·0	94·7
Control (group B)	88·8	87·4	83·2	78·7	76·6	77·1	80·8	79·5
S.E.D.M.	3·49	2·77	2·32	2·45	2·44	3·05	4·09	3·62
Significance (D.M./S.E.D.M. >2) ..	0·229	1·3	0·216	4·37	6·19	5·93	3·23	4·2
Average P.C.V. (%):								
Group D	39·3	38·1	37·3	37·7	37·8	38·3	39	38·4
Control (group B)	39·8	38·3	37·1	35·5	34·6	35·5	36·8	35·9
S.E.D.M.	0·884	0·825	0·818	0·712	0·706	0·808	0·91	1·09
Significance (D.M./S.E.D.M. >2) ..	0·566	0·242	0·244	3·09	4·53	3·47	2·42	2·29
Average M.C.H.C. (%):								
Group D	32·4	32·3	32·6	34·2	35·2	35·8	35	35·6
Control (group B)	32·4	33·2	32·4	31·9	32·2	31·5	31·8	32·3
S.E.D.M.	0·865	0·67	0·624	0·734	0·868	0·799	1·14	0·64
Significance (D.M./S.E.D.M. >2) ..	0	1·34	0·32	3·13	3·46	5·38	2·81	5·16

TABLE IV.—*Tolerance to Iron*

Group	Intractable Diarrhoea and Vomiting (Removed from Experiment)	Gastro-intestinal Symptoms (Persevered with Treatment)
A	6	6
C	3	3
D (mol-iron)	1	1

ferri et ammonii citras was even better tolerated and proved equally efficient. The mol-iron tablets are easier to prescribe and to take than this latter preparation, but the increased expense involved and the world shortage of molybdenum may delay the routine use of these tablets (which are now made in England). The important point to realize is that many pregnant women cannot tolerate ferrous sulphate pills and therefore do not take them.

This investigation suggests that a high percentage of pregnant women in Bradford suffer from iron deficiency, and that the administration of iron together with calcium and vitamin D prevents both the microcytic and the "physiological" anaemia of pregnancy. An idea to be considered further is whether iron deficiency may in some way be associated with the occurrence of miscarriage and hypertension (see Table V). The only disadvantage of maintaining the haemoglobin level at its normal value throughout pregnancy would

TABLE V.—*Additional Observations*

Group	Miscarriage	Hypertension (Blood Pressure Exceeding 140/90 mm. Hg on at Least 2 Occasions)	Post-partum Haemorrhage—More than 20 fl. oz. (570 ml.)
A	—	—	3 (one required blood transfusion)
Control (B)	2 {18 weeks, 28 "	5 (1 eclampsia)	1
C	—	1	1 (required blood transfusion)
D	—	1	1

appear to be a slightly increased risk of post-partum haemorrhage. We therefore conclude that the so-called "physiological" anaemia of pregnancy is in reality the expression of iron deficiency, and that the diet in Bradford, and probably in many other centres, is and is likely to remain deficient in this mineral. It would clearly be important to see whether the controlled administration of iron to a much larger group of women would decrease the high incidence of hypertension in pregnant women in Bradford, and whether the maintenance of the normal haemoglobin level throughout pregnancy is associated with the accepted figure for the increase in blood volume.

Summary and Conclusions

A review of haemoglobin readings obtained from 2,000 consecutive cases at or below the 16th week of pregnancy showed that about 60% were subnormal, and that 6.5% of the women were severely anaemic.

The changes in haemoglobin and packed cell volume readings which occurred during pregnancy in matched groups of young healthy women lead us to conclude that: (*a*) the "physiological" anaemia of pregnancy is associated with a low or subnormal mean corpuscular haemoglobin concentration; (*b*) normal (non-pregnant) blood values are maintained if therapeutic doses of ferrous sulphate are administered throughout pregnancy; and (*c*) the administration of ferrous sulphate, or of molybdenized iron, from the 24th to the 32nd week of pregnancy, results in recovery from the commencing "physiological" anaemia, followed by maintenance of normal (non-pregnant) blood values.

The mol-iron tablets were not found to be more efficacious than ferrous sulphate tablets either in preventing or treating the "physiological" anaemia of pregnancy, but they were better tolerated. We would suggest that ferrous sulphate is not a suitable preparation for the routine administration of iron in antenatal clinics.

We think that the controlled administration of iron to a large group of women should be undertaken in order to see whether the incidence of hypertension would thereby be lessened. It would also be of interest to determine whether the maintenance of the normal haemoglobin level throughout pregnancy is associated with the accepted value for the increase in blood volume.

We would like to thank Dr. R. G. Paley, of the department of medicine at Leeds University, who kindly studied the scheme and made most valuable suggestions from the statistical point of view.

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HAEMOGLOBIN LEVELS IN ADULTS AND CHILDREN

BY

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This paper reports the results of haemoglobin studies on 245 males and 266 females of adult age employed in clerical and industrial work, on 214 housewives under 60 years, all living in and around London, and on 1,628 boys aged 6, 10, and 14 years living in two Lancashire towns (I and K), one Surrey town (J), and one Gloucestershire town (L) (see Table I). The method was the same as that employed in earlier studies (Magee and Milligan, 1951), except that oxyhaemoglobin was the pigment determined instead of alkaline haematin. As before, many precautions were taken to ensure accuracy—the two photometers were re-checked by the National Physical Laboratory, pipettes were re-calibrated, and blood was drawn by finger-prick after a period of rest, depending on the previous state of activity of the individuals. The findings are expressed as grammes of haemoglobin per 100 ml. of blood, and, for comparison with previous findings, especially those of the M.R.C. 1943 Survey (M.R.C., 1945), as Hb% on the Haldane scale.

TABLE I.—*Haemoglobin Levels g./100 ml. and Percentages (Haldane), compared with 1943 Haemoglobin Survey*

Category	No.	Present Survey Mean and Standard Deviation (g. Hb/100 ml. Blood)	% Haldane and Standard Deviation	Mean 1943 Survey. % Haldane Scale
Adult Males				
A. Clerical workers	94	15·9±1·1	107·1±7·1	Mean of all married men 102·4, all single men 102·1
B. Factory ,,	100	15·6±1·0	105·5±6·9	
C. ,, ,,	51	15·5±1·1	104·9±7·3	
Total ..	245			
Employed Females				
D. Clerical workers	100	14·1±1·1	95·4±7·4	Mean for all manual working women 92·5, all unmarried 94·4
E. Factory ,,	101	14·1±1·3	95·0±8·7	
F. ,, ,,	65	13·6±1·4	91·8±9·2	
Total ..	266			
Housewives				
G. London borough	115	13·5±1·5	91·3±10·2	91·5
H. ,, ,,	99	13·6±1·2	91·9±8·3	
Total ..	214			
Schoolboys aged 6:				
Town I	147	13·1±0·8	88·8±5·6	Two samples, 87·1 and 94·0
,, J	150	13·8±1·0	93·0±6·8	
Schoolboys aged 10:				
Town I	196	13·5±1·0	91·2±6·6	91·0
,, J	133	14·0±0·8	94·2±5·7	
Schoolboys aged 14:				
Town I	176	14·3±0·9	96·8±6·0	Two samples, 97·6 and 97·9
,, J	190	14·7±1·0	99·5±6·5	
,, K	184	14·6±1·1	98·8±7·4	
Town L:				
1. Modern schools	211	14·6±0·9	98·7±6·5	,, ,,
2. Grammar ,,	165	15·0±0·9	101·5±6·1	,, ,,
3. Public ,,	76	14·9±0·7	100·5±5·1	,, ,,
Total ..	1,628			

Methods of Sampling

Adult males and females were selected at random; a letter was sent to every *n*th person on the roll of employees asking if he or she would co-operate; the refusal rate was low. No person of income above £1,000 per annum was included.

For housewives, streets were chosen at random and two constant house numbers in the street were nominated. If for some reason the housewife could not participate the house number adjoining was taken. The refusal rate was low. The tests were carried out in their own homes, and pregnant or lactating women and women over 60 were excluded, but no woman was excluded on the grounds of apparent ill-health. However, some housewives excused themselves from participating on health grounds. They numbered one-seventh of all refusals. Since, so far as we could judge, ill-health of a comparable degree existed among those housewives whose haemoglobin levels are reported here, we think that there is no bias from this cause.

For boys, the whole school population of the age groups 6, 10, and 14 years in certain schools, chosen for convenience, were examined.

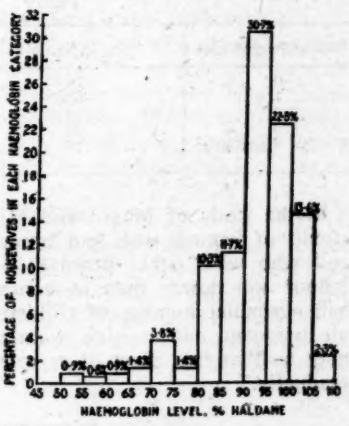
Results

Adult Males.—The mean haemoglobin level in clerical workers was slightly higher than that in manual workers (Table I). But the difference is not statistically significant, since it is less than twice its standard error. All three means are higher than those obtained in similar people in the 1943 Survey—102%. The higher value for the clerical workers in the present survey is in harmony with the findings of Adcock *et al.* (1948), who obtained higher values in sedentary men than in those of similar age receiving similar diets but engaged in more strenuous occupations—for example, the mean level for the Foot Guards was 99.9% and for R.A.M.C. hospital workers 103%. Adcock *et al.* did not make similar comparisons for women engaged in different occupations.

Adult Women.—The values obtained in the present survey for women show no consistent differences between the clerical and the manual workers, but it should be remembered that the occupation of the manual workers was far from strenuous. Taking the three groups of women (D, E, and F) as a whole, they compare favourably with the 1943 means for women manual workers and for unmarried women—92.5 and 94.4%, respectively.

Blood Donors.—There were 15 men and 28 women in the above groups (A–F) who had been blood donors for the National Blood Transfusion Service. Their mean haemoglobin levels were 104% for men and 94% for women. Among these were two men with haemoglobin levels of 104 and 111% and six women with levels of 86, 92, 92, 97, 100, and 86% who, for no disclosed reason, had been rejected on the last occasion they presented themselves for bleeding.

Housewives. — The means for the two groups of housewives (Table I) show no differences either between themselves or from the 1943 mean—91.5%. The distribution curve is negatively skewed (see Chart). The S.D. of the two groups is 9.65, which means that on a normal distribution 2.3% of the values would fall below 72.3% and 2.3% above 110.9%. There are no values above 110.9, but 5.6% of the total are below 72.3%. In practically all these women medical reasons for the low haemoglobin levels were elicited by questioning, and all of them were reported to their family doctors.



Percentage distribution of haemoglobin levels in 214 housewives.

Boys.—The haemoglobin determinations on boys were only part of a much more comprehensive survey which involved physical measurements, physical efficiency tests, medical examinations, inquiries into living conditions, and other socio-economic matters. A detailed analysis of the data, which will be published later, shows that where higher mean haemoglobin levels were observed they were merely one facet of a general physical superiority, which was reflected in larger stature, greater weight and strength, and an earlier onset of puberty. Among the socio-economic factors with which these differences were associated, non-dietary as well as dietary factors appear to be responsible. The various haemoglobin values compare favourably with those obtained in 1943 on boys of the same age.

Discussion

It has been suggested that the higher average haemoglobin level in male clerical workers (Group A) than in male manual workers (Groups B and C, Table I) is attributable to the, presumably, more active life of the latter. It might, however, be suggested that the difference is due to higher incomes and presumably better diets of the clerical workers. We were unable to obtain the incomes of Group A, but we found it for most men in Groups B and C. In Group B there was no relationship between income and haemoglobin levels. In Group C the mean haemoglobin of 16 men with incomes at or above £350 per annum was 106.4%, and of 22 men in the same group with incomes at or below £300 per annum, 103.7%. A similar relationship was found for employed women in Group F; 13 of these with incomes of £250 per annum or more had a mean of 94.9%, and 46 with incomes of £200 per annum or less a mean of 91.0%. These numbers are small, and an element of chance cannot, therefore, be entirely excluded. There would seem, however, to be some sort of relationship

between income and haemoglobin level, but this might be explained by the higher-paid workers being older and leading a more sedentary life than the lower-paid ones.

There was no evidence of a difference between the haemoglobin of married and that of unmarried men. Employed married women, on the other hand, had a higher mean level than spinsters in all three groups, D, E, and F, the differences being 0.65, 2.5 and 3.0%, respectively. These differences were found to be independent of income.

In 187 of the housewives the effect of parity could be investigated. Over the range 0–3 children no change in level was found, but the level for mothers of four or more children was well below that of the rest (Table II).

TABLE II.—*Haemoglobin Levels of Housewives According to Parity*

No. of Pregnancies	No. in Sample	Mean Hb % Haldane
0	14	90·2
1	62	91·4
2	64	90·8
3	31	91·7
4 and over	16	86·2

In the study of Magee and Milligan (1951) the haemoglobin of women who had borne three or more children and who were either pregnant or within 65 weeks after labour was lower than in comparable women who had had a smaller number of children. In the present survey all pregnant and nursing women were excluded, and it may be that this effect of repeated pregnancies disappears gradually.

Summary

Haemoglobin levels were determined in 245 adult men and 266 adult women employed in clerical and industrial work, on 214 non-pregnant and non-nursing housewives under 60 years living in and around London, and on 1,628 boys aged 6, 10, and 14 years living in two Lancashire towns (I and K), one Surrey town (J), and one Gloucestershire town (L). The mean findings are set out in Table I.

So far as they are comparable with the M.R.C. survey of 1943 the present findings are about the same or on a slightly higher level. Of the 214 housewives 5.6% had values less than 72.3% (Haldane). Medical reasons for the low levels were elicited by questioning.

Male clerical workers had higher values than male manual workers, a difference attributable to the more active lives of the latter. In some of the groups of men and women a direct relationship between income and haemoglobin level was observed; this difference may have been due to a more leisurely life in the higher income groups.

The haemoglobin level of boys of town I was lower than that of the boys of any of the other towns, and that of grammar and public school boys in town L was slightly higher than for modern school boys in the same city. The reasons for these differences in boys living in different parts of England and in different surroundings are being further investigated.

ADDENDUM.—Since writing the above, the doctors of women with Hb below 80% have tried the effects of iron therapy, in almost every case with satisfactory results. The proportion (8.9%) of women with Hb below 80% in this unselected sample and their ready response to iron medication suggests that the work of the general practitioner would be facilitated by routine Hb determinations in women patients. The colour of the mucous membranes, as reported elsewhere (Adcock *et al.*, 1949) may fail as an index of Hb level, but the Tallqvist method provides a simple and inexpensive means of ascertaining the Hb level with sufficient accuracy for practical purposes. This method was found by Macfarlane *et al.* (1948) to compare surprisingly well with other more complicated procedures.

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EFFECT OF VITAMIN-K PREPARATIONS ON HYPOPROTHROMBINAEMIA INDUCED BY DICOUMAROL AND TROMEXAN

BY

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The administration of dicoumarol (3,3′-methylene-*bis*-(4-hydroxycoumarin)) or "tromexan" (*bis*-3,3′-(4-oxycoumarinyl)-ethyl acetate) in the treatment of thromboembolic states may lead to severe or even fatal haemorrhage. Although careful control of treatment by repeated estimation of the blood prothrombin levels reduces this risk, a reliable and convenient antidote against such potent therapeutic substances would be of great value. Both dicoumarol and tromexan are anticoagulants by virtue of their causing hypoprothrombinaemia, and the two measures recommended to reverse this effect are the administration of preparations possessing vitamin-K activity and the transfusion of blood. There is no doubt that the latter treatment gives immediate and significant results, but for it to be most effective the blood must be in sufficient quantity. It is not always easy to meet this requirement, and reliance may be placed on the use of vitamin-K preparations such as are commercially available.

There is a measure of belief, based on experimental observations carried out during the past ten years, that these vitamin-K preparations are capable of reversing dicoumarol-induced hypoprothrombinaemia. From the available evidence at hand there can be no doubt that substances with vitamin-K activity do possess such powers, but there is still much confusion regarding the practical value of the various preparations which are available for this purpose.

It is hoped that the experiments described below will provide more conclusive evidence concerning the action and therapeutic value of these preparations.

Material and Methods

Either dicoumarol or tromexan was administered in therapeutic doses to patients in whom there was no obvious potential source of haemorrhage or evidence of hepatic, alimentary, or renal dysfunction. A test dose of the anticoagulant drug was given, and the effect on the prothrombin levels was observed at least daily. When the prothrombin levels had returned to normal, and had remained normal for two to three days, the same dose of the same drug was repeated, and a selected dose of a vitamin-K preparation was given. Plasma prothrombin levels continued to be estimated at least daily. In a few instances the technique was varied in respect of time of administration and of the number of the doses of vitamin K. The variations are indicated with the results in Table II.

The hypoprothrombinaemia expected from the anticoagulant therapy was not usually beyond customary therapeutic levels, as it was not considered necessary or justifiable to induce dangerous depletion of the plasma prothrombin.

TABLE I.—*Details of the Vitamin-K Preparations Tested*

Substance	Other Designation	Route of Administration	Dosage
2-methyl-3-phytyl-1:4-naphthoquinone	Vitamin K_1	Intravenously	200–340 mg. single doses
2-methyl-1:4-naphthoquinone	"Prokayvit" (B.D.H.); menaphthone; menadione	Intramuscularly	15–30 mg. in 2–3 days
2-methyl-1:4-naphthohydroquinone diacetate	Acetomenaphthone; oral prokayvit (B.D.H.)	Orally	90 mg. in 3 days
2-methyl-1:4-naphthohydroquinone carboxymethoxine	"Kapilon" (Glaxo)	Intramuscularly	60 mg. in 3 days
2-methyl-1:4-naphthohydroquinone diphosphate	"Synkavit" (Roche)	Intravenously	300–1,600 mg. in 3–4 days
Dipotassium 2-methyl-1:4-naphthylene bisulphate	Water-soluble K analogue (Boots)	,,	200 mg. i.v. single dose

Vitamin-K Preparations.—The vitamin-K substances which were tested, and their routes of administration, are shown in Table I. With the exception of vitamin K_1 these preparations are readily available commercially, and the doses of those which were given parenterally were limited only by the occurrence of untoward reactions. In the case of vitamin K_1, which is fat-soluble and which was received as an oily concentrate, a preparation suitable for intravenous administration was made as described by Davidson and MacDonald (1943). The oily fluid was dissolved in absolute alcohol (200 mg. K_1 in 4 ml. alcohol), and the solution was then added to 5% glucose (200–400 mg. K_1 in 500 ml.). The preparation was then autoclaved. Suspension of the vitamin in the glucose solution was assisted by injecting the alcoholic solution forcibly through a long fine needle into the centre of the bottle of glucose solution, but in spite of this the preparation tended to be unstable and had to be used almost at once. This preparation of vitamin K_1 was administered by intravenous infusion over a period of half to five hours without delay, otherwise the vitamin K_1 tended to settle out and adhere to the glass, with consequent loss of potency. No untoward reaction of any kind was encountered.

Estimation of Plasma Prothrombin.—Plasma prothrombin was estimated by the one-stage method of Quick. The same batch of rabbit-brain thromboplastin was used in each case, for the control and the test periods. The estimations were carried out on 100% and on 12.5% plasma. Only the figures obtained with 100% plasma are recorded here.

Results

The results of the various therapeutic trials of the vitamin-K analogues against the hypothrombinaemic effect of dicoumarol and tromexan are presented in Table II. In the case of vitamin K_1 the results of single tests are tabulated. In the case of the other preparations the average results from groups of patients are recorded: a more detailed analysis of these results is given below.

Vitamin K_1

Vitamin K_1 was tested against a single dose of tromexan in three patients. In the first case (Table II) 900 mg. of tromexan resulted in a prothrombin time approximately four times normal. The same dose of tromexan was given on the first day of the test period, and on the following day, when the prothrombin time had begun to rise, 200 mg. of vitamin K_1 was given intravenously. Within twenty-four hours the prothrombin time was 19 seconds, as compared with 60 seconds at this stage in the control period. In Case 2, 200 mg. of vitamin K_1 given at the same time as 900 mg. of tromexan appeared to act as a complete antidote. In Case 3

TABLE II.—*Effect of Dicoumarol and Tromexan on Plasma Prothrombin Time and the Modification of this Effect by Vitamin-K Analogues*

	Days of Control and Test Period					Remarks
	1	2	3	4	5	
	sec.	sec.	sec.	sec.	sec.	
Case 1	16 (T)	32	60	25	—	Control. T=900 mg. tromexan. K=200 mg. vitamin K_1 i.v.
	15 (T)	28 (K)	19	16	—	
,, 2	20 (T)	30	22	18	—	Control. T=900 mg. tromexan. K=200 mg vitamin K_1 i.v.
	19 (TK)	18	20	20	—	
,, 3	17 (T)	36	26	—	—	Control. T=900 mg. tromexan. K=340 mg vitamin K_1 i.v.
	21 (TK)	20	19 (T)	38	—	
,, 4	17 (D)	19	28	33	25	Control. D=400 mg. dicoumarol. K=200 mg. vitamin K_1 i.v.
	20 (D)	22	28 (K)	19	19	
,, 5	19 (D)	19	28	33	25	Control. D=400 mg. dicoumarol. K=300 mg. vitamin K_1 i.v.
	16 (DK)	19	22	19	19	
,, 6	17 (T)	22 (T)	40 (K)	12	—	T=600+300 mg. tromexan. K=300 mg. vitamin K_1 i.v
,, 7	—	75 (T)	75 (TK)	to 21 in 6 hours		T=Maintenance 300 mg. tromexan/day. K=300 mg. vitamin K_1 i.v.
Group 8 (5 cases) ..	16 (T)	25	28	—	—	Control T=900 mg. tromexan M=10 mg. menaphthone i.m.
	16 (TM)	21 (M)	23	—	—	
Group 9 (5 cases) ..	16 (T)	24	28	21	—	Control. T=900 mg. tromexan. AM=300 mg. acetomenaphthone
	18 (TAM)	26 (AM)	21 (AM)	16	—	
Group 10 (2 cases) ..	16 (D)	20	22	21	—	Control. D=200 mg. dicoumarol. AM=30 mg. acetomenaphthone
	18 (DAM)	22 (AM)	22 (AM)	21	—	
Group 11 (5 cases) ..	16 (T)	25	22	18	—	Control. T=900 mg. tromexan. K=20 mg. kapilon i.m.
	18 (TK)	22 (K)	22 (K)	18	—	
Group 12 (3 cases) ..	15 (D)	19	26	29	—	Control. D=200–400 mg. dicoumarol. K=20 mg. kapilon i.m.
	16 (DK)	24	22	20	—	
Group 13 (6 cases) ..	15 (T)	24	28	12	—	Control. T=600 mg. tromexan. S=100 mg. synkavit i.v.
	16 (TS)	24 (S)	20 (S)	11	—	
Group 14 (5 cases) ..	15 (D)	20	28	25	—	Control. D=200 mg. dicoumarol. S=100 mg. synkavit i.v.
	15 (DS)	16 (S)	28 (S)	20	—	
Group 15 (1 case) ..	18	18 (T)	31	23	18	Control. T=1,200 mg. tromexan. S=400 mg. synkavit i.v.
	18 (S)	18 (TS)	29 (S)	22 (S)	19	
Group 16 (1 case) ..	16 (T)	42	34	17	—	Control. T=1,200 mg. tromexan. B=200 mg. water-soluble analogue (Boots)
	17 (TB)	40	29	18	—	

the effect of 900 mg. of tromexan was likewise blocked by simultaneous administration of 340 mg. of vitamin K_1. As an additional check on the method of testing, this patient was given a further dose of tromexan without vitamin K_1. Hypoprothrombinaemia resulted.

Vitamin K_1 was tested against a single dose of dicoumarol in two patients. In the first of these (Case 4) the administration of 200 mg. of vitamin K_1 on the third day of the test period was followed by return of the prothrombin time to pre-treatment levels within twenty-four hours. In Case 5 the simultaneous administration of 300 mg. of vitamin K_1 was almost completely effective in blocking the action of 400 mg. of dicoumarol.

As a further test of the action of vitamin K_1 (Case 6) 900 mg. of tromexan was given over two days. On the third day, when the prothrombin time was 40 seconds, 200 mg. of vitamin K_1 was given intravenously. The prothrombin time fell to 30 seconds in two hours, and to normal within twenty-four hours. Case 7 illustrates the effect of 300 mg. of vitamin K_1 on a persistently high prothrombin time (75 seconds) occurring in a patient who was given 300 mg. of tromexan daily for several weeks for therapeutic purposes. In spite of the administration of the usual daily dose of tromexan, vitamin K_1 produced a rapid fall in the prothrombin time to 21 seconds within six hours.

From these investigations it is evident that when 200–340 mg. of vitamin K_1 was given at the same time as a reasonable therapeutic dose of tromexan or dicoumarol the action of the anticoagulant drug on the plasma prothrombin levels was completely, or almost completely, inhibited. When the vitamin was given at any time after hypoprothrombinaemia had been induced, the prothrombin levels were restored to normal in 24 hours. Furthermore, significant reduction of the prothrombin time occurred within an even shorter period, and safe values were achieved within six to nine hours even when previously the hypoprothrombinaemia had been more severe than is usually considered necessary for therapeutic purposes.

Menaphthone and Acetomenaphthone

The average results of the intramuscular administration of menaphthone (Group 8, Table II) suggest that this substance had an incomplete inhibitory effect on mild hypoprothrombinaemia induced by tromexan. In this group the individual test results and the control results were practically identical.

Acetomenaphthone was given orally to seven patients, to five who had received tromexan, and to two who had received dicoumarol. The average figures for those given tromexan (Group 9) suggest that the response to the anticoagulant was modified slightly by the acetomenaphthone. The individual results indicated that the effect of this vitamin-K analogue was slight and inconstant. Acetomenaphthone was tested against dicoumarol in two patients (Group 10). In each the test curve and the control curve were identical. Although larger doses of menaphthone and acetomenaphthone might well have been given by mouth, it was felt that oral treatment was unsuited to this purpose and no further observations were made with acetomenaphthone. Dosage of menaphthone was limited by pain which followed the intramuscular injection.

Kapilon, Synkavit, and Water-soluble K Analogue (Boots)

Kapilon was tested against tromexan in five patients (Group 11, Table II). In no case could it be said that kapilon given intramuscularly in doses of 20 mg. daily for the first three days significantly affected the response to tromexan. Kapilon was tested against dicoumarol, which was given in doses of 300 mg. During the test period kapilon was given in doses of 20 mg. on the first and third days. In all three patients slight but significant modification of the prothrombin response occurred. In no case, however, did the prothrombin time return to normal within three days of administration of the first dose of kapilon.

Synkavit, given intravenously in doses of 100 mg., was tested against tromexan in six patients (Group 13). In five of these the control and the test curves were practically identical. In the sixth case of this group slight modification of the response occurred during the test period. Synkavit was tested against doses of dicoumarol, which produced prothrombin times of 30–40 seconds, in five patients (Group 14). Each patient was given 100 mg. of synkavit daily for the first three days of the test period, and in no case was there any demonstrable effect on the prothrombin-time curve. As an additional test of the action of synkavit, even larger doses were given (400 mg. intravenously), beginning on the day before the administration of tromexan (Group 15) and continuing for a further three days. No modification of the action of the tromexan was demonstrated: the control curve and the test curve were identical.

Water-soluble K analogue (Boots) was tested against tromexan in one patient. Given intravenously in a dose of 200 mg. it slightly modified the effect of the anticoagulant (Group 16) but failed to reduce the prothrombin time to normal within 24 hours.

The various water-soluble vitamin-K analogues have thus been shown to be relatively inactive against the hypoprothrombinaemic effect of tromexan and dicoumarol. Although in some instances—notably the tests of kapilon against dicoumarol—an effect was demonstrated, this effect was insufficient to prevent a fall in plasma prothrombin concentrations as a result of the administration of a single relatively small dose of the anticoagulant. That the lack of effect is not merely a matter of dosage of the vitamin-K analogue is indicated by the complete failure of 1,600 mg. of synkavit given over a period of four days to modify the normal therapeutic effect of a single dose of tromexan.

Discussion

Among all the vitamin-K analogues tested against dicoumarol and tromexan in this investigation the only substance which was uniformly significantly active was vitamin K_1. This material was given intravenously in doses of 200–340 mg., and it was almost invariably completely effective in blocking or in reversing the action of the anticoagulant under the circumstances of the test. The other substances tested did occasionally modify the effect of the anticoagulant, but the effect was inconstant and slight. Comparable doses were not always given, but, from the practical point of view, oral administration of vitamin K is unlikely to be satisfactory as an emergency treatment, and, given by other routes, the doses of menaphthone and synkavit were limited by local or general reactions.

In the present investigation no attempt was made to give doses of anticoagulants which would result in dangerously low prothrombin levels. It might therefore be considered that the tests do not give information directly applicable to the treatment of the hypoprothrombinaemic emergency. On the other hand, this would merely point to some doubt about the value of vitamin K_1 under more exacting conditions, and the immediate result of administering it to a patient with a prothrombin time (100% plasma) about four times normal (Case 7, Table II) without stopping the tromexan administration is good evidence of the potency of this substance even in very adverse conditions. As regards the other analogues, the relatively small dosage of the anticoagulant employed serves to emphasize the inefficiency of these vitamin-K preparations.

During the past 10 years considerable interest has been shown in the effect of vitamin-K analogues on dicoumarol-induced hypoprothrombinaemia, and numerous experiments have been carried out both in animals and in the human subject. It cannot be said, however, that there is general agreement about either the relative effects of the various vitamin-K preparations or the form of vitamin-K activity which is most suitable for the treatment of hypoprothrombinaemic bleeding occurring as the result of the administration of dicoumarol or tromexan.

This lack of agreement has probably been due to two variable factors. In some experimental trials water-soluble vitamin-K preparations were regarded as effective when the anticoagulant was given in minimum active quantities. There is good evidence that this is so (Shapiro *et al.*, 1943), but little that they are effective against therapeutic doses of dicoumarol. The second variable factor has been the expected response to administration of vitamin K. Many writers have considered adequate a response demonstrable in the course of days and have been content to advise the use of the water-soluble preparations. Our own findings on the inadequacy of these preparations and the greater reliability of vitamin K_1, together with evidence presented by others on the use of vitamin K_1 or its oxide, seem to justify the conclusion that there are only two known effective means of treating hypoprothrombinaemia induced by dicoumarol or tromexan. These are by transfusion of blood or by administration of vitamin K_1 or its oxide.

In view of the fact that transfusion, to be effective, involves the use of blood or of frozen fresh plasma from possibly more than a single donor, and that thereby delay may often occur in beginning adequate treatment, there is some justification for regarding a suitable preparation of vitamin K_1 or its oxide as an essential material in any department in which treatment by dicoumarol or tromexan is being carried out. Neither vitamin K_1 nor its oxide is available commercially, but it could doubtless be made so, and, as has been shown (Shoshkes *et al.*, 1950), a convenient, effective, and stable emulsion can be prepared for intravenous use. No reliance should be placed on the use of larger doses of the synthetic water-soluble vitamin-K analogues. The action of vitamin-K preparations against the hypoprothrombinaemic effect of dicoumarol or tromexan is not simply a matter of dosage. There is a difference in the action of water-soluble and oil-soluble preparations which has not so far been explained except that it has been related to the presence of the "phytyl" group in the molecule of vitamin K_1 (Miller *et al.*, 1950).

Summary and Conclusions

The effect of certain substances with vitamin-K activity in modifying the action of dicoumarol and tromexan has been investigated in the human subject. The vitamin-K preparations employed were vitamin K_1, menaphthone, acetomenaphthone, kapilon, synkavit, and water-soluble K analogue (Boots).

Apart from vitamin K_1, these substances have been shown to possess a minor and inconstant ability to modify the action of these anticoagulants. Vitamin K_1, on the other hand, is a reliable and efficient antidote, and is capable of completely blocking the action of therapeutic doses of dicoumarol and tromexan, and capable of restoring to safe levels within a few hours excessive hypoprothrombinaemia due to these drugs.

Since these differences between the vitamin-K preparations are not merely a question of dosage, of all the substances tested here only vitamin K_1 can be regarded as a reliable antidote for a hypoprothrombinaemic emergency.

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ACQUIRED SENSITIVITY TO *PARA*-AMINOSALICYLIC ACID

BY

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Since the widespread use of *para*-aminosalicylic acid (P.A.S.), either by itself or in conjunction with streptomycin, in the treatment of pulmonary tuberculosis, reactions have occurred which indicate that it is possible to distinguish two groups of cases.

First there are those patients with a natural intolerance to P.A.S. who develop gastro-intestinal symptoms during the first few days of treatment. As reported by Lehmann (1947) nausea is the symptom most frequently encountered, and may be accompanied by vomiting and diarrhoea in cases which exhibit a greater intolerance to the drug. Nagley and Logg (1949) pointed out that these effects are often due to impurities in the preparation of the drug and are seldom so severe as to cause abandonment of P.A.S. therapy.

Secondly, there are a few patients who develop an acquired allergic sensitivity to P.A.S. In these cases the onset of symptoms is characteristically sudden and usually occurs between two and four weeks after the beginning of treatment. Drug fever, with a rise of body temperature to 100–103° F. (37.8–39.4° C.), and symptoms of a marked constitutional disturbance are the usual features of this type of reaction and are commonly accompanied by a pruritic skin eruption as reported by Kierland and Carr (1949). Other toxic effects which have been recorded include renal damage (Nagley and Logg, 1949), hepatitis and enlargement of lymphatic nodes (Cuthbert, 1950), and lowering of the serum potassium (Cayley, 1950).

Case Report

The following case of an unusually severe sensitivity reaction to P.A.S. recently occurred at the Brompton Hospital.

A draughtsman aged 29 was admitted with the following history. He had developed pulmonary tuberculosis involving the right lung in 1944, for which he was treated by rest for 10 months at the Royal National Sanatorium, Ventnor. During this time a right artificial pneumothorax was induced, but this was abandoned after two months owing to the formation of an effusion. He subsequently returned to work and remained well until January, 1951, when, following a febrile coryza, he had a sudden haemoptysis of about 1 oz. (28 ml.).

Treatment consisted of rest in bed at home, and in March he began treatment with P.A.S., 18 g. daily by mouth. Three weeks later he had an evening rise of temperature, followed in two days by nausea, vomiting, and headache, and four days later by a morbilliform rash and pyrexia rising to 104° F. (40° C.). P.A.S. was discontinued, and the pyrexia and rash subsided on treatment with mepyramine hydrogen maleate ("anthisan").

One week later, while still receiving mepyramine, 100 mg. thrice daily, he was given two 3-g. doses of P.A.S., and within six hours the temperature rose to 102° F. (38.9° C.) and the rash returned. Despite discontinuation of P.A.S. the pyrexia and rash persisted, and five days later there was tender enlargement of the cervical, axillary, post-occipital, inguinal, and epitrochlear lymphatic nodes accompanied by sore throat, epigastric pain, and tenderness. The following

day he was clinically jaundiced, with a tender liver enlarged to 1 in. (2.5 cm.) below the costal margin. The rash, which became confluent on the face and neck while remaining morbilliform on the trunk, was accompanied by severe pruritus. The spleen was not palpable.

Investigations.—Urine: No albumin; excess urobilinogen and a small amount of bilirubin present. Serum bilirubin 4.5 mg. per 100 ml. Direct positive Van den Bergh reaction. Paul–Bunnell test, negative without absorption. Wassermann reaction and Kahn tests, negative. A blood count showed: Hb, 73%; red cells, 4,100,000; C.I., 0.9; white cells, 14,300 per c.mm. (polymorphs 34%, lymphocytes 48%, monocytes 2%, eosinophils 15%, basophils 1%).

Treatment was changed to diphenhydramine hydrochloride ("benadryl"), 50 mg. four times daily, and he responded with slow but steady improvement. Calamine lotion successfully relieved the pruritus. Within 10 days the temperature fell by lysis, the glands mostly subsided, clinical jaundice disappeared, and the liver became normal in size and no longer tender.

During the first week of treatment with benadryl the rash faded, pruritus ceased, and desquamation began on the face and neck, followed by desquamation on the trunk during the second week and on the arms and legs during the third week. Some glandular enlargement of the inguinal and axillary groups persisted until the desquamation on the limbs was complete.

By the end of the third week the serum bilirubin was 1.3 mg. per 100 ml., and the white blood cells numbered 16,400 per c.mm., but the lymphocytosis had subsided and the eosinophilia showed a decrease (polymorphs 60%, lymphocytes 20%, monocytes 10%, eosinophils 8%, basophils 2%).

Patch Tests.—At the conclusion of treatment, when clinically no manifestation of the sensitivity reaction remained, patch tests were performed (see Table). Two cases were selected as controls. Control 1 was a patient who had never received P.A.S. Control 2 was a patient receiving P.A.S., 18 g. daily, who had shown no manifestations of sensitivity.

Patch Tests

Test	Patient Before Desensitization	Patient After Desensitization	Control 1	Control 2
Aqueous solution of P.A.S 5% ..	++	0	0	0
Chloroform ..	0	0	0	0
Aniline	++	+	0	0
Para-aminobenzoic acid	+	0	0	0
P.A.S. 5% solution in chloroform ..	+++	0	0	0
Meta-aminophenol	++	0	0	0
Benzoic acid ..	0	0	0	0
Salicylic acid ..	+	0	0	0

For these tests P.A.S. was prepared as a 5% solution and the other reagents as equimolecular solutions in chloroform.

Desensitization.—The patient was successfully desensitized by giving graduated doses of P.A.S. by mouth. A single dose of 50 mg. was given on the first day, and this was increased by 50 mg. each day in divided doses. If pyrexia occurred the dose was halved the following day and then increased as before from the reduced level. When the daily dose of P.A.S. reached 1 g. it was increased by 0.5 g. each day until a satisfactory therapeutic dosage of 15 g. daily was obtained. After desensitization the patch tests (see Table) were repeated; they proved negative with the exception of a doubtful positive reaction to aniline.

Discussion

Patients who show intolerance to P.A.S. or associated impurities should be distinguished from those who develop an allergic sensitivity by the differences described above in the mode of onset and severity of the reaction. Early recognition is important, because P.A.S. therapy may be continued safely despite mild gastro-intestinal symptoms, but should be withdrawn immediately if an allergic sensitivity develops, as otherwise it may be practically impossible to control the reaction.

Antihistamine drugs are generally found useful in the treatment of the sensitivity reaction once P.A.S. has been withdrawn, but, as Horne (1949) observed, they are insufficient to control it if P.A.S. therapy is resumed before the patient has been desensitized. Once sensitivity has developed, even a small dose of P.A.S. is enough to provoke a severe reaction. Madigan *et al.* (1950) reported this effect after a dose as small as 0.5 g. In the case reported above two 3-g. doses of P.A.S. were given after the patient had become sensitized, and, despite an adequate dosage of an antihistamine drug being maintained, a reaction of considerable severity occurred.

In sensitized patients, skin tests usually show a positive reaction to dilutions of P.A.S. of 5% and upwards and to dilutions of *meta*-aminophenol of 1% and upwards, as observed by Climie (1950). Positive results are still obtained with patch tests even after the clinical termination of a sensitivity reaction. After desensitization, however, patch tests become negative in most cases, although Climie reported a persistent reaction to *meta*-aminophenol.

The method of performing skin tests may influence the results obtained. The technique used in the cases reported here consists in applying to the skin a measured quantity of the reagent in solution in chloroform by means of a pipette and drying it in a current of air. The area is then covered with adhesive plaster, which is removed after 24 hours, and readings are made at 48 hours. This method has been found to give accurate results, and is relatively simple to carry out.

Patients who have developed sensitivity may be desensitized by giving small quantities of P.A.S. by mouth and gradually increasing the dose. A scheme beginning with 0.1 g. of P.A.S. daily was suggested by Madigan *et al.* (1950); this will improve the tolerance of the patient by slow stages until an effective daily dosage of P.A.S. is reached. In desensitizing the case reported above it was considered advisable, in view of the severity of the reaction, to use a modified method beginning with 50 mg. daily, and to increase the dose of P.A.S. more gradually up to the required therapeutic level of 15 g. daily.

Summary

A severe case of P.A.S. sensitivity is described. The manifestations were pyrexia, sore throat, pruritus, morbilliform rash, generalized glandular enlargement, jaundice, hepatomegaly, and epigastric pain, accompanied by a marked lymphocytosis and eosinophilia.

The response to antihistamine drugs and to desensitization is recorded.

Skin tests with P.A.S. and certain related chemical compounds were positive, but became negative after successful desensitization. The technique used for these tests is described.

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RELATION BETWEEN SENSITIVITY TO THIOPENTONE, SULPHONAMIDES, AND SUNLIGHT

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Intravenous injection of thiopentone is a very frequent and, in experienced hands, safe procedure in both anaesthetic and narcoanalytical practice. Sensitivity reactions occur infrequently, Davidson (1943) mentioning two instances in 9,000 injections. We have administered over 15,000 injections in surgical and psychiatric practice and have encountered the three cases of sensitivity reported here. Two of these involved not the scarlatiniform rash commonly seen in these uncommon cases but angioneurotic oedema, and the other showed a less developed form of the syndrome. We wish to call attention to these uncommon reactions, which could, if unprepared for and unexpected, lead to grave difficulties, especially when encountered in the consulting-room as opposed to the operating theatre. We also wish to correlate our findings with other apparently relevant evidence concerning sensitivity to sulphonamide compounds encountered therapeutically.

Case 1

A single woman aged 26 had received 15 injections of thiopentone (0.15–0.35 g.) over a period of six months from January, 1948, in the narcoanalytical treatment of the depressively coloured anxiety state associated with very severe insomnia, from which she had suffered for five years. Response to treatment had been satisfactory. Injection of thiopentone caused sleep for three to seven minutes followed by a prolonged drowsiness, without signs of sensitivity. In April, 1950, a further narcoanalytical session was occasioned by a recurrence of symptoms, and subjective relief was obtained. In May she again presented herself for narcoanalytical treatment. The day had been very sunny, but naturally she did not mention the fact that she had exposed her face and arms for 20 minutes at 3 p.m., two hours before the injection (during which no perivenous leakage occurred) of 0.35 g. of thiopentone.

Five minutes after the end of the injection, as she was rousing from the deepest sleep, her face became brilliantly red and minor restless movements of the head and neck occurred. Restlessness increased and within three to five minutes the forearms and elbow regions were reddened, the patient clasping the lower abdomen. Marked urticaria appeared above the elbows, and colic and numbness of the lips were complained of in a hoarse voice. Her face and eyelids were swollen, and pitting oedema was present over the radius. Twelve minutes after the injection the pulse was thin and thready, the rate being 146. A diagnosis of angioneurotic oedema was made, and adrenaline, 7 min. (0.4 ml.), was given subcutaneously at the rate of 1 min. (0.06 ml.) a minute with no good effect. At this stage the eyelids were beginning to evert and the eyes were completely closed. The lips and the tongue were swollen, and tenderness and pain were felt in the throat as well as in the abdomen; but breathing was not embarrassed, and cyanosis was absent.

One tablet of mepyramine hydrogen maleate ("anthisan") was taken with difficulty. Calcium gluconate, 10 ml. of 10% solution, was injected into the vein at the rate of 1 ml. a minute. By the time that 6 ml. had been administered subjective relief was noticed and erythema was subsiding. As the distribution of the skin reaction was so reminiscent of sulphonamide sun-sensitivity, the patient was asked at this point whether she had been sitting in the sun earlier in the day. A hoarse affirmative answer was obtained. Abdominal cramps persisted for a further 10–15 minutes. The blood pressure was 136/78 at the end of the injection of calcium gluconate, the pulse having fallen steadily from 156 to 110 during the time of the injection. She then began to feel cold and started to shiver, but this passed off in about ten minutes. One and a half hours after the injection of thiopentone she had recovered, apart from feeling rather shaken, drowsy, and muddle-headed.

Case 2

A woman aged 60 suddenly developed haematuria (due to papilloma of the bladder) associated with transient oedema of the lip while on holiday in Canada. After her return to England and during the succeeding four or five years she was at intervals submitted to intravenous anaesthesia on seven occasions, for purposes of cystoscopy and diathermic cautery of the papilloma. Premedication on the first three occasions was with "omnopon," 1/3 gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.). Hexobarbitone ("evipan") was used for the first two operations with no untoward sequelae. Thiopentone, 0.5 g., was used on the third occasion, its initial exhibition being followed by a red papilliform rash of the thorax and neck, and erythema of the face. Post-anaesthetic itching occurred. Some months later a second injection of thiopentone was followed by a similar reaction, with, in addition, transient mild angioneurotic oedema of the lips, which subsided spontaneously. Hexobarbitone was again used uneventfully for the fifth anaesthetic, but on the sixth occasion, in the absence of hexobarbitone, a different brand of thiopentone was used. Again the cutaneous reaction, with angioneurotic oedema, was elicited, and was well controlled by antihistaminics by mouth. On the seventh and most recent occasion hexobarbitone was given and the patient recovered uneventfully.

Case 3

A married woman aged 33, suffering from obsessional neurosis with anxiety hysteria, uneventfully received thiopentone, 0.25–0.35 g., intravenously on more than 40 occasions (at weekly intervals), reacting with sleep of one to three minutes, followed by drowsiness. After an interruption of treatment for six weeks, cough and laryngeal tickling appeared during the recovery of consciousness, and were at first thought to be due to an incipient cold which was later associated with nasal catarrh. Recovery from thiopentone, however, continued to be associated with cough and laryngeal discomfort after the infection had passed, and in a few weeks there occurred a red blotchy condition of the face and neck which persisted for 20 minutes or so. Systemic disturbances and itching were absent. Substitution of a sulphur-free intravenous barbiturate ("cyclonal sodium" brand of hexobarbitone) in place of thiopentone in equivalent dosage (0.6–0.8 g.) was followed by uneventful recovery from the induced sleep.

Comment.—These three cases illustrate sensitivity to thiopentone, and Cases 2 and 3 suggest very strongly that the sulphone radical is involved. Case 1 is, we believe, the first recorded instance of photosensitivity to thiopentone. It was, in fact, this case which prompted a search of the literature for similar cases, and led to a review of sensitivity to barbiturates and photosensitivity to sulphonamides.

Literature and Discussion

Barbiturate sensitivity, though uncommon, may manifest itself somatically (when it usually takes the form of a maculo-papular rash, possibly associated with systemic disturbance and pyrexia) and/or psychically (as excitement,

delirium, or collapse). The literature on angioneurotic oedema after barbiturates is small and scattered. Hunter (1943) briefly describes urticaria after incision of a septic finger under thiopentone, and mentions angioneurotic oedema after hexobarbitone, quoting Hewer (1939) in support. We found reference in Hewer only to angioneurotic oedema after pentobarbitone, which is of interest in view of Case 2. Hunter's main case is of idiosyncratic systemic reaction to thiopentone in an R.A.F. officer who had previously reacted normally to inhalation anaesthesia. From his description, the lesions appear to be restricted to the areas exposed to the sun (cf. sulphonamide sensitivity and Case 1). In Davidson's (1943) two cases the sensitivity consisted of scarlatiniform rashes, with transient pyrexia.

Knauss (1946) describes urticaria following dental extraction under thiopentone in a man aged 41 who had, a month earlier, uneventfully undergone the same procedure but with a preliminary local injection of adrenaline. Peterkin (1946) describes the occurrence of purpuric reactions of the trunk following thiopentone anaesthesia on three occasions in a man who had previously and uneventfully received inhalation anaesthesia. Following this, Warren (1946), R. H. Moore (1946), and P. H. Moore (1946) each described a case. In all three cases urticaria developed—in one instance after hysterectomy in a tuberculous patient, and in another in a man (who had 40 times uneventfully received thiopentone with or without inhalation anaesthesia in connexion with a perineal wound) when he was given 1 g. of thiopentone. In this case a subsequent administration of 0.5 g. of thiopentone combined with inhalation anaesthesia passed off uneventfully. Apart from these six cases mentioned in the literature, Lundy (1942) makes passing mention of the occurrence of urticarial reaction in thiopentone anaesthesia.

While it is recognized that barbiturates produce skin-sensitivity reactions, photosensitivity seems much less common. Stryker (1939) describes the case of a child aged 2 who developed an exfoliative dermatitis after receiving barbiturate for six weeks. Four months later the child developed an acute dermatitis of the exposed areas after playing in the sun, and was found to be excreting barbitone and porphyrins in the urine. Stryker quotes Schulzberger as considering barbiturates capable of giving rise to photosensitivity.

A local vesicular eruption (possibly generalized and exfoliative) is the commonest form of skin-sensitivity reaction to sulphonamides, and is most readily evoked by repeated topical application. Urticarial photosensitivity was noticed in Middle East troops, and Peterkin (1945) found 72% of 500 cases of sulphonamide dermatitis to be photosensitive. Watkinson and Hillis (1947) discuss the relationship between oral sulphonamides, sunlight, and the pustulation stage of vaccinial lesions in R.A.F. personnel. They found the highest incidence of sulphonamide photosensitivity associated with the pustulation stage of the lesion. Where vaccination did not take, or was refused, photosensitivity did not occur, even though exposure to sunlight and ingestion of sulphonamides were the same in all troops. They support Erskine's theory that toxins liberated from a buried focus are causative of photosensitivity.

Park and Platts (1942) described photosensitivity in 3.4% of (mainly ambulant) men exposed to strong sun and receiving oral sulphonamides. In a case of acute tonsillitis an unusually severe skin rash developed on the first day of oral sulphonamide (as opposed to the usual 8th–10th day), the rash being concentrated in the areas exposed to the sun, even though the last exposure had been three days earlier. They regard this case as having "photo-allergy" (Epstein, 1939), although Epstein's criteria are apparently not fulfilled. (These are solar reaction without oedema preceding injection of sulphonamide, and followed in ten days by spontaneous development of oedema at the site of injection, or elsewhere, or an earlier oedematous reaction in response to solar irradiation, provided that a certain "critical" amount of sulphonamide has been injected.) Porphyrin excretion has not been fully investigated in the current literature (owing to circumstances), although the significance of coproporphyrin I as a photosensitizer is well recognized. Its presence in the excreta of patients taking sulphonamides was pointed out by Rimington and Hemmings (1938), who also mention that sulphonal may evoke photosensitivity and promote the excretion of coproporphyrin I. They compare the clinical pictures of acute porphyrinuria and sulphonamide intoxication. The present paper may indicate the connexion between sulphonamides and thiobarbiturates with regard to sensitivity reactions.

Burckhardt (1948) has shown that burning, tanning, and specific photosensitivity provocation occur independently of each other at different light wavelengths, and that photosensitive reactions occur only in the areas actually irradiated by the provocative wave-band. Local tissue damage and, in some cases, systemic effects analogous to toxic reactions are characteristic of sunburn, and are in keeping with the presence in the circulation of a substance derived from tissue damage (? histamine-like, ? porphyrin-like). Systemic reactions generally last less than three days, and pigmentation usually begins after this time. Skin repeatedly exposed to ultra-violet radiation is less likely to burn even in the absence of pigmentation.

Correlating these observations, we put forward the hypothesis that skin-sensitivity reactions here considered depend upon the interaction of the following factors. (1) Tissue damage, as septic focus, mechanical trauma, local infection, or interference with tissue metabolism—for example, by drugs. (2) The presence of the sulphone radical, either as thiobarbiturate or as sulphonamide, locally applied or given by mouth or injection. Depending on the intensity of these two factors, local or general reactions may result. (3) Sunlight may act as a form of factor 1 when the burning effect is marked, and hence may be sufficient with factor 2 to produce a non-photosensitivity reaction. The longer rays may also, acting with factor 1 and/or factor 2, trigger off a true photosensitivity reaction. These reactions occur when a critical level (Epstein) is overstepped. The double role of sunlight seems to resolve the discord mentioned by Urbach and Gotlieb (1946) concerning skin colour and sulphonamide photosensitivity, on the basis of acclimatization to the burning rays of the sun as opposed to the tanning rays.

The case (Park and Platts, 1942) of tonsillitis shows the synergism of local tissue damage and circulating products from the throat, and in this instance the rash is described as photosensitive. From Park and Platts and from Watkinson and Hillis it is clear that skin areas not submitted to solar exposure or to mechanical trauma—for example, the bathing-drawers area—are never involved in sulphonamide photosensitivity, whereas the ischial tuberosities of bedridden patients are more susceptible than those of ambulant cases. In Case 1, a patient who burned easily in the sun, recent exposure had occurred, and presumably breakdown products were circulating. This would account for the local and general symptoms, on the hypothesis advanced above. Similarly, in Case 2 the focus of tissue damage was a necrosing papilloma of the bladder.

Clark (1943) describes a case, clearly illustrative of the interaction of local and general factors, in which the sequence was as follows: first four days, successful local treatment of skin lesion with sulphonamide in strong sun; ten days later sulphathiazole by mouth precipitated an acute reaction in the areas exposed to the sun, followed by secondary infection, for which seven days later he was given sulphadiazine by mouth, provoking a generalized scarlatiniform rash; six weeks later, after recovery, local sulphathiazole provoked a local reaction, and on the following day oral sulphathiazole provoked a reaction in the sun-exposed areas; ten weeks later local application of sulphathiazole provoked a local reaction.

It is perhaps relevant to point out here that in surgical practice thiopentone is usually given if established tissue damage exists and hence tissue-breakdown factors are

circulating. This would account for the tendency to the generalized form of sensitivity reaction. All the cases from the literature cited in this paper showed significant tissue damage related to general reactions.

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TERRAMYCIN IN INFECTIONS IN INFANTS AND CHILDREN

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"Terramycin" is a new antibiotic obtained from *Streptomyces rimosus*, an actinomycete isolated from the soil (Finlay *et al.*, 1950). Its physical and chemical properties have been studied by Regna and Solomons (1950), and it has been shown to be a stable, amphoteric substance of high potency (Linsell and Fletcher, 1950). Preliminary experimental studies (Hobby *et al.*, 1950) have shown that it is active both *in vitro* and *in vivo* against a wide variety of pathogenic organisms. It is effective against Gram-positive and Gram-negative bacteria, spirochaetes, rickettsiae, and certain of the larger viruses, yet is distinguished by its low toxicity (Finlay *et al.*, 1950; King *et al.*, 1950; Herrell *et al.*, 1950).

Terramycin is supplied in 50, 100, and 250-mg. capsules of the crystalline hydrochloride salt, and as a yellow crystalline powder which dissolves easily in a specially prepared cherry-mint-flavoured liquid to make an elixir ("terrabon") suitable for administration to infants and children. A special solution containing 25 mg. of terramycin as the crystalline hydrochloride, made up with 62.5 mg. of sodium chloride and 25 mg. of sodium borate, dissolved in 5 ml. of distilled water, is available for ophthalmic use.

This report is based on a study of the use of terramycin in various infections of infancy and early childhood. Sixty-six children were treated with this drug, no other therapy being given during its administration. The dosage was 50 mg. per lb. (450 g.) of body weight per day, the elixir being given by mouth at six-hourly intervals for a period of seven days to each of 54 patients. It was found to be extremely palatable, and no difficulties were encountered in its administration. In fact, ward sisters preferred its use to other antibiotics because it was taken so readily by infants and children. Routine white-cell estimations during the course of treatment did not show any depressant action on the total count or on the polymorphonuclear elements. The special ophthalmic solution was used for the treatment of 12 newborn babies, and was instilled into the eyes in the following manner: one drop every minute for five minutes, followed by one drop every two minutes for ten minutes, the whole procedure being repeated three times a day.

Terramycin was used for the treatment of pneumonia (35 cases), upper respiratory tract infections (10 cases), tonsillitis (6 cases), pyuria (3 cases), and purulent conjunctivitis (12 cases).

Pneumonia

The 35 cases of pneumonia, all confirmed radiologically, showed the following age distribution:

0–5 months	6 cases	2 years	6 cases
6–11 „	7 „	3 „	5 „
1 year	11 „		

Nasopharyngeal swabs were cultured in every case, the predominating organism being shown in Table I.

TABLE I.—*Predominating Organism on Culture of Nasopharyngeal Swab*

Organism	No. of Cases
Streptococcus viridans	7
Streptococcus haemolyticus	5
Pneumococci	6
Staphylococcus pyogenes	2
Haemophilus influenzae	1
Friedländer's bacillus	1
Normal flora—no predominating organisms	13

In 23 cases the temperature fell to normal within 24 hours, in seven cases fever disappeared in 48 hours, and in one case in 72 hours. Improvement in appetite, colour, and general condition coincided with the settling of the temperature. Radiological clearing of the lungs usually took a few days longer than the disappearance of clinical signs.

One child, aged 3½ years, with a right lower lobe pneumonia, presenting characteristic clinical and radiological findings, showed no response to treatment until the dose was doubled and 100 mg. per lb. (450 g.) body weight per day was given. In this case the defervescence occurred by lysis over a period of eight days. No response to the drug was obtained in three patients (Table II), one of whom died.

TABLE II.—*Details of Three Cases Not Responding to Terramycin*

Case No.	Sex	Age	Dose	Diagnosis	Nasoph. Swab	Result
1	F	5/12	125 mg. 6-hrly for 7 days	R.L.L. pneumonia	*Staph. pyogenes*	Responded to "aureomycin"
2	F	3 yr.	250 mg. 6-hrly for 7 days	Broncho-pneumonia (coeliac disease)	Pneumococci	„ „
3	M	6/52	100 mg. 6-hrly for 7 days	Broncho-pneumonia	Friedländer's bacilli; pneumococci; *Str. haemolyticus*	Death. Necropsy showed collapse of left lower lobe, consolidation of right middle and lower lobes with abscesses. Pus: Friedländer

Upper Respiratory Tract Infections

Ten children with upper respiratory tract infections, classified as rhinopharyngitis, laryngitis, and otitis media, responded similarly to those in the pneumonia group, with an improvement in the clinical condition and a return of temperature to normal in 24 hours. In one child with otitis media, the discharge from the ear ceased within 24 hours, but the other ear then suppurated. Both ears were completely dry within five days of the onset of therapy.

Tonsillitis.—Six children with tonsillitis improved within 24 to 48 hours of treatment.

Pyuria

Three children with pyuria were treated. One, aged 8 weeks, with a staphylococcal perinephric abscess, had improved after surgical drainage and penicillin therapy. Three weeks later, however, he developed an acute febrile illness due to a *Bact. coli* pyuria. Sulphonamide therapy produced a temporary improvement, but during the subsequent five months he showed two further episodes of urinary infection, each controlled by sulphonamides and streptomycin. A further recrudescence at the age of 8 months, due to a coliform infection superimposed on a non-functioning left kidney, was treated with terramycin, and after seven days' treatment the urine showed no pus on microscopy or organisms on culture. During a follow-up period of four months he has had no recurrence of pyuria.

The second patient, aged 2 years 10 months, had suffered for two years from recurring bouts of pyuria associated with a left megalo-ureter. Sulphonamides, streptomycin, and chloramphenicol in turn had produced only temporary improvement. Terramycin therapy has so far maintained the urine bacteria-free for the longest period to date, about six months.

The third patient, aged 2 years, developed recurrent attacks of pyelitis associated with a congenital abnormality of the left kidney. The infecting organism, *Bact. coli*, responded at first to streptomycin, but became resistant after one course of therapy. Three further episodes of pyuria cleared up quickly with terramycin, but improvement was maintained for short periods only. The organism, however, is still sensitive to this antibiotic.

Conjunctivitis

Twelve newborn babies with purulent conjunctivitis were treated with terramycin. Swabs of the purulent material were cultured. In each case a coagulase-positive *Staphylococcus aureus* was grown, and its sensitivity to penicillin, streptomycin, and terramycin determined. Six out of seven cases classified as mild, three classified as moderate, and two severe cases improved within 48 hours, as shown by cessation of discharge and disappearance of injection of the conjunctivae. Although many of the mild cases of conjunctivitis will clear up without antibiotic therapy, terramycin is useful in those cases requiring antibiotics but in which the organism has become resistant to penicillin and/or streptomycin. No evidence of clinical irritation due to the drug was noted.

TABLE III.—*Cases of Conjunctivitis*

Case No.	Type	Organism	Sensitivity			Results
			Penicillin	Streptomycin	Terramycin	
1	Mild	Coag.-pos. *Staph. aureus*	Resistant	Sensitive	Sensitive	Improved
2	,,	,, ,,	Sensitive	,,	,,	,,
3	,,	,, ,,	,,	,,	,,	,,
4	,,	,, ,,	Resistant	,,	,,	,,
5	,,	,, ,,	,,	,,	,,	,,
6	,,	,, ,,	Sensitive	,,	,,	,,
7	,,	,, ,,	Resistant	,,	,,	*
8	Moderate	,, ,,	Sensitive	,,	,,	Improved
9	,,	,, ,,	,,	,,	,,	,,
10	,,	,, ,,	Resistant	Resistant	,,	,,
11	Severe	Coag.-pos. *Staph. A.* + *Str. viridans*	,,	,,	,,	,,
			Sensitive	,,	,,	
12	,,	Coag.-pos. *Staph. aureus*	Resistant	,,	,,	,,

* Did not improve on terramycin. Responded to streptomycin.

Discussion

The broad antimicrobial spectrum of terramycin, combined with its low toxicity, ease of administration, and rapid absorption from the gastro-intestinal tract, suggests that this new drug is a most useful addition to chemotherapy. In contradistinction to penicillin and streptomycin, which have to be given by injection, and to aureomycin and chloramphenicol, which, although given by mouth, are distinctly unpalatable, terramycin can be given in a pleasant form by the oral route. It is therefore particularly valuable in paediatric practice. Although a large number of reports on its use have already appeared in the American literature, opportunity of using the drug in this country has so far been limited, and no account of its value against the common infections of infancy and childhood has yet appeared.

Friedländer's bacillus is highly sensitive to the action of terramycin *in vitro* (Gunnison *et al.*, 1950), but so far no report describing its clinical effects in this type of infection has come to our attention. Hobby (1950, personal communication) mentioned three of five adult patients who showed complete resolution of lung consolidation within five days of the beginning of therapy. In our series, one infant with a Friedländer bronchopneumonia died.

Wooding and Scott (1951) reported the successful use of terramycin in 10 cases of bacterial pneumonia in infants and children, while Graves and Ball (1951), comparing the action of aureomycin, chloramphenicol, and terramycin in a series of 143 children with atypical pneumonia, considered terramycin to be the drug of choice in the treatment of this disease.

Two patients developed a scarlatiniform rash mainly involving the trunk and accompanied by a slight rise of temperature on the third day after cessation of treatment. As no other drugs had been given, it is assumed that this was a drug rash due to terramycin. Vomiting, diarrhoea, glossitis, and moniliasis were not seen. The "ano-rectal syndrome" described by Willcox (1951) in male adults treated for gonorrhoea was not noted.

Summary and Conclusions

A group of 66 infants and children with various infections were treated with terramycin, using a dose of 50 mg. per lb. (450 g.) body weight per day. Thirty-four out of 35 patients with pneumonia responded rapidly to treatment, in most cases within 24 hours. One patient with a Friedländer's bacillus pneumonia died.

Ten patients with upper respiratory tract infections, six with tonsillitis, and three with pyuria also showed a rapid and dramatic response. Eleven out of 12 infants with purulent conjunctivitis responded rapidly to the drug.

There were no toxic reactions, and it is stressed that terramycin, because of its wide spectrum of antibacterial activity and, in the form of the elixir, its easy and palatable administration, is particularly valuable in paediatric practice.

Grateful acknowledgments are due to Dr. Gladys L. Hobby, of Messrs. Charles Pfizer and Co. Inc., Brooklyn, New York, for generous supplies of terramycin, and to the physicians at the Duchess of York Hospital for Babies, Manchester, for permission to treat patients under their care. We wish to thank Professor Wilfrid Gaisford for advice in the preparation of this paper.

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Medical Memoranda

Addison's Disease and Pregnancy

Pregnancy in patients with Addison's disease is unusual, and before the introduction of "eucortone" and "doca" it was almost invariably fatal (Perkins, 1932). More recently cases successfully managed through pregnancy have been described (Thom *et al.*, 1941, 1942; Sheldon, 1945; Zwanenberg, 1945; Simpson, 1946; Knowlton *et al.*, 1949). Crises may occur in the early stages due to vomiting, but, once these have passed, the patients usually remain well until after delivery. In the first few days of the puerperium, however, crises of acute adrenal insufficiency are frequent. Hypoglycaemia may also be a serious complication, and irreversible coma may occur. Knowlton *et al.* (1949) recommend stabilization throughout the pregnancy with daily injections of intramuscular doca to allow for requirements which vary in the different stages. Little extra salt is advised, to give a wider margin of safety should vomiting occur and salt ingestion be discontinued. After delivery, intravenous glucose saline, 1 to 2 litres, and additional eucortone, 20 to 40 ml., are given daily.

CASE REPORT

A woman aged 35 was diagnosed as a case of Addison's disease in 1945. The diagnosis was based on the presence of typical pigmentation, including generalized brown discoloration of the whole skin, slaty-coloured patches in her mouth, a deep brown areola around each nipple, and pigmentation of scars. Her blood pressure at this time was 100/68 mm. Hg, and she was complaining of tiredness and of attacks of vomiting. A Kepler test was not performed, but serum sodium and potassium levels were estimated at times when she was thought to show signs of increasing adrenal insufficiency, and in 1949 these showed levels of 215 mg. and 32 mg. per 100 ml., respectively. She was maintained on implants of doca, 200 mg. being inserted every three to six months as she became deficient.

She was maintained in fairly good health until December, 1949. Then, in spite of an implant of 200 mg. on November 12, she noticed increasing weakness and vomiting. At the beginning of January, 1950, she was thought to be pregnant, because of amenorrhoea since November 4, and was admitted to hospital because of severe vomiting. In spite of her dehydration, a rapid pulse, and a blood pressure of 70/40 mm. Hg, her urine contained 14 g. of salt per litre (measured by Fantus's method). Intravenous saline was given, her daily salt intake was increased to 15 g. a day, and eucortone, 20 ml. daily, was given for three days.

After discharge from hospital in January she felt tired and unwell, and vomiting continued to be troublesome. The doca was therefore supplemented by intramuscular injections of an oily solution of doca, 5 mg. twice a week. At the 14th week of her pregnancy there was slight blood loss per vaginam, and she was thought to have a threatened miscarriage. This was treated by rest in bed, and at the same time she was stabilized on a daily maintenance dose of doca intramuscularly. This was increased to 10 mg. a day gradually, and her salt was reduced to 3 g. a day, her blood pressure remaining about 105/70. After discharge from hospital she was maintained fairly well on twice-weekly injections of 30 mg. of doca.

On June 8 she was admitted to hospital because of abdominal pains. From the size of the fundus twins had been suspected, and their presence was confirmed radiologically. On June 9 spontaneous delivery of male twins occurred. Delivery was premature at the 34th week, the infants being very underweight. One, weighing 2 lb. 12 oz. (1.2 kg.) at birth, has survived, the other died of asphyxia.

After delivery a 5% glucose saline drip was set up, 2 to 3 litres being given daily for four days. Doca intramuscularly, 10 mg. a day, was continued, and supplementary eucortone to guard against a crisis. The blood pressure, however, was well maintained at a higher level than before delivery, and on the fourth day signs of electrolyte and fluid retention occurred, with the development of a lumbar pad. Eucortone and salt were therefore discontinued and doca was stopped for 24 hours. She was re-stabilized on doca, and was found to need 5 mg. a day. On July 19 400 mg. of doca was implanted in the erector spini muscles. Lactation began after delivery, but was rapidly inhibited by oestrogen.

Since delivery the mother and the surviving infant have remained well. The patient has, however, had three mild hypoglycaemic attacks, with faintness associated with hunger; each occurred while she was working before dinner. An oral glucose-tolerance test showed a normal curve, but an intravenous glucose-tolerance test showed marked hypoglycaemia three hours after the injection. She has been taking more frequent small carbohydrate meals since this time, and has been free from attacks for three months.

Comment.—Thorn *et al.* (1940) have shown that most patients with hypoglycaemic symptoms have a normal oral glucose-tolerance curve. Many, however, react abnormally to an intravenous glucose-tolerance test in which 0.5 g. of glucose per kg. is given during half an hour; hypoglycaemia develops three to four hours later.

I wish to thank Dr. D. H. G. MacQuaide for his assistance in preparing this paper and also Mr. G. Sturtridge, who undertook the obstetric management of the patient.

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A Case of Interstitial Tubal Pregnancy

Individual cases of interstitial pregnancy are of sufficient interest and rarity to deserve attention. When such a case is associated with symptoms and signs even more puzzling than usual, it serves to re-emphasize the difficulty in diagnosis; when, in addition, a study of the case reveals an almost astonishing recurrence of ectopic implantation the details would appear to merit publication.

All writers agree on the rarity of the condition. Bethel Solomons (1949) described a case, the third in his own experience, and quotes Grusetz and Polayes (1944), who collected a total of 199 cases from the literature up to the year 1943. Wynne, in 1918, collected 1,547 cases of ectopic pregnancy and found that there were 18 cases of the interstitial variety, an incidence of 1.16%. MacFarlane and Sparling (1946) found seven cases in a series of 106. MacVine and Lees (1949) stated that at least two of the more severe forms of ectopic pregnancy were interstitial in a series of 107 cases extending over a 10-year period. Thus the incidence would appear to be in the region of 1% to 2% of all ectopic pregnancies reported, and this figure is in agreement with that quoted by Keenan (1944). This figure, however, seems very high and is probably an exaggeration, for, as Johnstone (1928) has pointed out, there must be many series of tubal pregnancies numbering 100 or more but containing no example of the interstitial variety.

CASE REPORT

A 3-gravida 2-para aged 29 was admitted as an emergency case on June 13, 1949. She gave a history of three normal menses following cessation of lactation of her second child, born March 26, 1948. After her last period on March 23,

1949, there had been amenorrhoea until May 24, when a brown offensive vaginal discharge suddenly began without antecedent pain or apparent cause. Two days later there occurred a very profuse vaginal haemorrhage with the passage of many clots. After 24 hours she was able to get up and carry on her household duties, but the loss continued "like the first day of the period" until her admission to hospital three weeks later. Five days before admission she experienced her first attack of abdominal pain. It was central in distribution and a continuous ache in character, being exacerbated by sudden movement, defaecation, and micturition. There had previously been no bowel or micturition symptoms.

The patient's menstruation was normally regular, with a cycle of 30 days and loss of seven days. The menarche had occurred at 16. There had been two normal deliveries, in 1938 and 1948.

The letter from her private doctor contained an outline of the relevant past medical history, and the details were later supplemented by the previous case notes and by correspondence with the hospital concerned. In 1939 appendicectomy was performed in the Bristol General Hospital and convalescence was delayed by peritonitis and wound sepsis. In 1943 right salpingo-oophorectomy was carried out at the Radcliffe Infirmary, Oxford, for chronic salpingo-oophoritis. In November, 1946, she was again operated upon in Bristol for a right ectopic pregnancy. Unfortunately, detailed clinical notes cannot be traced, but there is definite evidence that a right ectopic pregnancy had apparently ruptured into the broad ligament and was densely adherent to the right wall of the uterus, to bowel, and to omentum. The available notes made no mention of the right salpingo-oophorectomy performed three years previously.

Examination on admission revealed a tired, flushed, ill-looking woman. Her temperature was 99° F. (37.2° C.), pulse 90, respirations 20, and blood pressure 125/80. General examination and urinalysis were negative. Her breasts showed equivocal signs of pregnancy. The haemoglobin was 92%. The abdomen was scarred by previous laparotomies. No tumour was palpable, and there was no definite tenderness. There were no signs of free fluid. On vaginal examination the vulva and vagina and their mucosal colouring were normal. The cervix was softened and the os closed; movement was painless, and there was slight bleeding. The uterus was bulky and retroverted, and there was an extremely tender pulsating mass in the pouch of Douglas.

In spite of the unusual history the examination suggested that in the main the most likely diagnosis was that of ectopic pregnancy, but the differential diagnosis was a wide one. The patient was prepared for laparotomy.

Examination under anaesthesia after catheterization confirmed the pre-operative findings. The uterus was anteverted and the pulsating mass could then no longer be felt. After dilatation of the cervix, curettage revealed exuberant endometrium and a sensation of fullness in the region of the right cornu. A large-bore needle was passed through the posterior fornix and frank blood in quantity was readily aspirated. At laparotomy there was a moderate amount of old and recent blood in the peritoneal cavity. The uterus was slightly enlarged and blood was spurting from the site of a ruptured right interstitial pregnancy. The ragged bleeding cavity measured 4 by 3 cm. The anatomy of the right round ligament was normal, but the Fallopian tube and ovary were absent on that side. The left tube was normal, and the ovary contained a corpus luteum. The affected area of the fundus was excised by a V-shaped incision and the uterus refashioned with catgut sutures. The scar was peritonized by a loop of the round ligament. It was particularly noticed that there was no communication between the gestation sac and the cavity of the uterus.

Convalescence was stormy, being interrupted by episodes of paralytic ileus on the second day, wound sepsis on the seventh day, and a discharge of watery purulent material from the vagina on the seventeenth day after operation. Vaginal examination at this time revealed no abnormality. With sulphonamide and penicillin the temperature settled and the abdominal wound healed soundly. The ileus responded to the usual treatment. The patient was finally discharged 24 days after operation.

The pathologist reported that the specimen, on section, showed a haemorrhagic cavity lined in places by pale clear cells of decidual appearance. No chorionic villi were demonstrated in the sections taken. There was deposition of calcium in the myometrium, and also evidence of myometritis and a salpingitis in the remaining portion of the interstitial segment of the tube.

COMMENT

The difficulty of diagnosing with any certainty an interstitial ectopic pregnancy before operation is well known, and this case was no exception. It is presumed that embryo death and a curiously asymptomatic intraperitoneal rupture took place about May 26—facts compatible with the size of the cavity found at operation. The fresh haemorrhage from the cavity seen on inspecting the uterus was probably occasioned by the preliminary anteversion. The microscopical appearance of a myometritis and interstitial salpingitis was an interesting feature of this case and explained the purulent discharge per vaginam, the wound sepsis, and, partly at least, the post-operative pyrexia.

But perhaps, above all, the case described is exceptional because it demonstrates clearly that on two separate occasions the fertilized ovum transmigrated across the pelvis to become ectopically implanted each time in that portion of the tube remaining after two separate salpingectomies. In Keenan's paper on interstitial pregnancy is mentioned the finding by D'errico of 23 cases of such pregnancy occurring in the stump following the removal of the extrauterine portion of the tube. Such behaviour is an eloquent testimony to the bizarre insistence and persistence of the reproductive function in woman, and it is a reminder of the pitfalls attendant on any operative procedure on the tube devised for the purpose of sterilization.

My thanks are due to Mr. H. L. Shepherd for his permission to publish this case, to Miss M. O. Dunster for her courtesy and help, and to Dr. A. L. Taylor for his pathological report.

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The West Middlesex Hospital has for many years been helped by a considerable body of voluntary workers in a great variety of ways (*Third Annual Review*, July, 1950–October, 1951, South-west Middlesex Hospital Management Committee). To co-ordinate the work of these helpers and to give formal recognition to their services a League of Friends of West Middlesex Hospital has been formed. Activities of its members include the sewing on of buttons and tapes in wards, singing and playing to elderly patients, visiting patients without relatives or friends, and help with preparations for special occasions such as Christmas festivities. Members of the Women's Voluntary Services have continued to provide a trolley-shop service in the wards, and they also run a canteen trolley for out-patients. Help of this kind is very much appreciated both by patients and hospital staff, says the report, and the value of the work done by these voluntary workers cannot be over-emphasized. It is hoped that they will continue to give their services and enrol their friends.

Reviews

THE KIDNEY

The Kidney: Medical and Surgical Diseases. By A. C. Allen, M.D. (Pp. 584; 1,115 illustrations. $15 or £5 5s.) New York: Grune and Stratton. London: J. and A. Churchill. 1951.

This is an important book by an acknowledged authority on the pathology of the kidney. It embodies the latest and, in the opinion of the reviewer, the most successful attempt to correlate the clinical and biochemical aspects of renal disease with structural changes in the kidney. In a series of brilliant and fascinating studies, which include much original work, the author succeeds in demonstrating not only that morbid histology is an active and growing science with much yet to contribute to knowledge of renal disease, but that morphology is still the rock upon which a sound understanding of these disorders must be based. Even such contentious entities as diabetic glomerulosclerosis, haemoglobinuric, osmotic, and cholaemic nephrosis, and the renal complications of disseminated lupus erythematosus and toxaemia of pregnancy, for example, are seen to fall naturally into a logical, if for clinical usage perhaps a trifle cumbersome, system of classification based on morbid histology. The evidence is nowhere strained in order to produce an all-embracing classification, and where gaps occur they are carefully pointed out.

The book includes chapters, in addition to those on the various forms of Bright's disease, on such subjects as embryology, anatomy, normal and abnormal physiology, uraemia, malformations, infections, pyelonephritis, calculi, renal rickets, and tumours, and a useful section on histological artifacts. Each chapter is an accurately informed and balanced review of current knowledge in which the author's personal views, though never obtruded, are clearly apparent. There is a carefully selected bibliography at the end of each chapter, and an adequate subject index concludes the volume. The 1,115 illustrations have been skilfully chosen and most beautifully reproduced. No one interested in the kidney can fail to profit from reading this book, and the author and publishers are to be congratulated on a valuable addition to the literature on the kidney and its disorders.

A. A. OSMAN.

ACTION OF ANAESTHETICS

The Mode of Action of Anaesthetics. By T. A. B. Harris, M.B., B.S., D.A., F.F.A.R.C.S. (Pp. 768; 64 tables, 22 figures. £2 2s.) Edinburgh: E. and S. Livingstone. 1951.

It is immediately evident that Dr. Harris has devoted an immense amount of time and thought to the production of this book, and no experienced anaesthetist could fail to peruse its 700 pages without learning a great deal about the theoretical aspects of his specialty. Each chapter concludes with a copious list of references, while a comprehensive index of 67 pages enables any subject to be tracked down with ease and rapidity.

He discusses at great length the chemistry and biochemistry of the subject, sometimes in terms which are unfamiliar to the average anaesthetist, and the addition of a glossary might be advantageous. The theories advanced are most stimulating to thought, but the beginner should not take them all too seriously or he may become nervous of administering any anaesthetic at all. In some places the author tends to describe the action of drugs as they should be according to current theory rather than as they actually are. For example, few senior men would agree with the description of the cardiovascular effects of cyclopropane and trichlorethylene, although the described effects *may* occasionally be seen and certainly fit in very nicely with the *expected* actions from a consideration of their structural formulae and physical properties. Again, the theory that toxicity increases with the number of chlorine atoms in the molecule is not borne out by experience with isopropyl chloride and trichlorethylene, nor is the suggestion that the jactitations during administration of nitrous oxide are associated with a build-up of carbon dioxide. The idea that cauda equina lesions following spinal analgesia are due to the deposition of the analgesic base is ingenious, but it seems much less likely to be true than the accepted explanation of contamination of the injected solution by the antiseptic in which the ampoules have been kept.

These few examples are not to be regarded as destructive criticism but show how provocative of thought this volume may be. The type and general production are excellent, but shorter paragraphs and more cross-headings would make the text easier to follow.

C. LANGTON HEWER.

ENZYMES

The Enzymes. Chemistry and Mechanism of Action. Edited by James B. Sumner and Karl Myrbäck. Volume 2, Part 1. (Pp. 790. $14.80.) New York: Academic Press, Inc. 1951.

This is the third part of this work, the first volume of which (in two parts) has already been reviewed (*Journal*, June 30, 1951, p. 1493). As with the previous parts, each chapter has been prepared by an authority on the subject under discussion. This first part of Volume 2 opens with an erudite and elegant treatment of the theory of oxidation reduction, by the late Dr. Leonor Michaelis, whose classic work in this field is known to all students of enzymology. Then follow four chapters on enzymes which bring about the fission of phosphate-containing substances, the first by N. O. Kaplan on thermodynamics and mechanism of the phosphate bond, the second by Sydney P. Colowick on transphosphorylating enzymes of fermentation, the third by H. M. Kalckar on dephosphorylation of adenosine polyphosphates, and the fourth, on aldolase and isomerase, by Otto Meyerhof. These chapters bear witness to the importance which the biochemist places on "energy-rich phosphate bonds" and their role in the storage of chemical energy and in the processes whereby energy is made available for many different metabolic processes.

The remainder of the chapters cover decarboxylases, co-enzymes, flavin-containing enzymes, iron-containing enzymes, copper-containing oxidases, and enzymes concerned with the metabolism of amino-acids and amines, with the oxidation of unsaturated fats, and with sulphur compounds. The volume closes with chapters on "Anaerobic Glycolysis, Respiration and the Pasteur Effect," by Frank Dickens, and on "Yeast and Mold Fermentations," by F. F. Nord and Sidney Weiss.

It will be seen from the titles how wide is the field covered by the 790 pages of the 21 chapters of this book. Unfortunately, since this book is only the first part of Volume 2, there is no index, and until the second part of Volume 2 is published some inconvenience in the use of the present book will be met with by those who wish to utilize it for general reference. The production of the book is good and the diagrams and illustrations are clear, but it is hardly one to be read by those who wish to browse in the field of enzymology. As an instalment of an encyclopaedic work of reference in the field of enzymes it will find a worthy place on the shelf beside its predecessors.

F. G. YOUNG.

BLOOD DISEASES

Handbook of Diseases of the Blood. By A. Piney, M.D., M.R.C.P. (Pp. 213; illustrated. £1 1s.) London: Harvey and Blythe. 1951.

A patient with a blood disease may quite possibly be seen first by a physician, diagnosed by a clinical pathologist, and treated by a surgeon or a radiotherapist, and in most British hospitals the clinical pathologist holds the key position in this team. Much time and money is spent on the investiga-

tion of patients with obscure and incurable blood disorders, and some people feel that the money would be better used on fundamental research and the prevention of disease. Dr. Piney's complaint, however, is that the system has led to the neglect of bedside observation of patients with blood disorders. He has therefore written this book to supply an almost entirely clinical account of the blood diseases, laboratory aids being described only when they are essential to amplify the results of clinical observation.

Working within this frame of reference, he has produced a book which will be useful to students going up for the higher examinations in medicine. The first chapter is on the symptoms of diseases of the blood and the second on the haematological signs. The actual diseases are then discussed in sequence. The book is lucidly written and well printed. Nevertheless, to those who associate Dr. Piney's name with illustrated books on haematology it will be something of a disappointment, and one cannot help feeling he would have made a better book if he had fused together the material and illustrations in his recent *Synopsis of Blood Diseases, Sternal Puncture*, and the present volume. If the student is going to read a separate text on haematology, then he had better get a complete but not too detailed synoptic account, such as Fowler's *Hematology*. Dr. Piney, by restricting his gaze to half the picture, would seem to be in danger of widening the division he deplores.

L. J. WITTS.

HORMONE ASSAY

Hormone Assay. Edited by C. W. Emmens. (Pp. 556; illustrated. $10.00.) New York: Academic Press Inc. 1950.

The field of biological standardization has increased so rapidly in the last fifteen years that it is no longer possible to comprehend the subject within one book of reasonable size. Dr. Emmens has therefore performed a valuable service by editing a volume on hormone assay, which is a well-defined section of the field, and he has chosen his eighteen contributors with great care. It is interesting to note that eight are from the U.S.A., six are from Britain, three are from Australia, and one is from Denmark.

The reader unfamiliar with the subject will find the book formidable, for the methods are presented by many of the writers with so much statistical matter that the ordinary physiologist or biochemist would find it difficult to follow them. It seems as if the worker in biological standardization has found some statistical treatment essential, and, having mastered a little, has developed an appetite for more and has finally acquired a vocabulary which, while as clear as daylight to him, makes his speech seem like a foreign language to others. It is a pity that this should have happened, since workers in biological standardization have made a great contribution to the design of biological experiments and to assessing the value of the results. The mathematical caution with which they regard their findings could be extended widely with much benefit.

The difficulty arises from the introduction of technical terms. A scientific worker ought to be forbidden to introduce a new technical term unless he has obtained permission from a suitable tribunal, or by the majority vote of a large society, except when the term is self-explanatory. Take the words "analysis of variance." No worker in biological standardization dare admit to-day that he does not understand what it means. Yet how many physiologists understand it? If I quarrel with my neighbour I am "at variance" with him. Has "analysis of variance" anything to do with that? The work of those who are engaged in research is of value only so far as it becomes known to others and understood by them. It can be understood only if it is not shrouded in technical terms. The introduction of a new technical term is therefore not a matter of pride; it should bring a sense of failure that a further obstacle has been put in the way of common intercourse.

The contributors to Dr. Emmens's book are a distinguished group. It is difficult to single them out, but the articles by Dr. R. I. Dorfman on androgens and on adrenal cortical hormones and by Dr. R. K. Callow on the chemical assay of steroids should be specially valuable to many workers.

J. H. BURN.

CHEST OPERATIONS

Thoracic Surgery. By Richard H. Sweet, M.D. Illustrations by J. R. Arroyo, M.D. (Pp. 345; 155 figures. £2 10s.) Philadelphia and London: W. B. Saunders Company. 1950.

This book sets out nakedly and unashamedly to be what it is—a handbook of chest operations for those surgical artisans who wish to operate on or within the chest. The author gives a fine display of illustrations, designs for operations, and complete tables and summaries of procedures. As would be expected from a surgeon of Dr. Sweet's eminence and ability, he performs his task admirably.

Discussion of the surgery of the thorax, as opposed to mere operating, is scanty, but there are several remarks which are either controversial or reveal the imperfection of the purely technical presentation. The author states that the Semb apicolysis is of no use if the lung is at all rigid. It is disturbing to read that the only aftercare needed for a drained empyema is wound dressing; no mention is made of physical treatment and none of control with pleurograms. We are also informed that chronic empyema is a rare sequel. Would it were so! Also, *horribile dictu*, the Schede operation is revived and described. We are told by word and picture that the best site to divide an adhesion in a case of artificial pneumothorax is midway between its lung and chest-wall attachments. These are almost the only features that one can criticize adversely. The section on the oesophagus is excellent.

It is noteworthy that such a frankly vocational book should have come from the Harvard School of Medicine, whose primary interest is usually in the more academic principles of medicine and surgery. Perhaps Dr. Sweet will later delight us with a second volume on the pure surgery of his craft. In the meantime this volume can be highly commended and strongly recommended to those who wish for a guide to operations upon the thorax.

R. C. BROCK.

ANATOMY FOR NURSES

Applied Anatomy for Nurses. By E. J. Bocock, S.R.N., S.C.M., D.N., and R. Wheeler Haines, M.B., D.Sc., F.L.S. (Pp. 320; 231 figures. 15s.) Edinburgh: E. and S. Livingstone. 1951.

This book is in several respects unusual. The authors describe elementary anatomy and, to a certain extent, the "application" of it, though not so much as the title would lead the reader to expect. In addition they give quite a considerable amount of elementary physiology and histology in language which is clear and sometimes colloquial. Here and there one gleans some interesting and out-of-the-way information—for example, why eunuchs do not go bald, and why osteopathy is incorrect. The illustrations are mostly diagrammatic and explanatory; there are a few which might be called crude. The authors are, we hope, unfair to the surgeon in thinking that a chronic psoas abscess could be mistaken for a local boil or an abscess of the lymph nodes, for a psoas abscess is painless.

The most unusual part of the book is the appendix, which concerns the supply of bodies for dissection. The authors emphasize the urgent need for them, and "it seems fair to ask nurses both to donate their bodies for dissection and to persuade others to do so in suitable cases." This would be a noteworthy form of applied anatomy.

There is certainly much to be learnt from this book.

V. ZACHARY COPE.

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BACTERIAL RESISTANCE TO CHEMOTHERAPY

The clinical exploitation of a new antimicrobic drug passes usually through two main phases, the first being over-enthusiastic and somewhat indiscriminate, and the second more critical and restrained. One factor in this transition is often the discovery that some strains of an otherwise susceptible organism are, or are apparently becoming, resistant to the drug. This change rapidly reduced the efficacy of sulphonamides in gonorrhoea, and showed signs of threatening the usefulness of these drugs in pneumonia and in streptococcal infections before a powerful reinforcement arrived in penicillin. Of the proportion of these and other bacteria now insensitive to sulphonamides very little is known, but examination of strains of some bacteria from unsuccessfully treated urinary tract infections clearly shows their capacity to acquire resistance. Penicillin has withstood the test of time much more successfully, but it is unfortunate that the one species, *Staph. pyogenes*, which seems to be slowly escaping from its influence is that against which its action was perhaps of the greatest value. Resistance to streptomycin can be acquired so quickly by any species that it stands in a class apart, and the diminishing use of this drug for treating any condition other than tuberculosis is due in part to the increasing prevalence of resistant organisms, although the fashion for the newer antibiotics has been another influence. So far as resistance is concerned it seems that chloramphenicol, "aureomycin," and "terramycin" have a good deal in common: resistance to one—which can certainly develop, although sometimes only to a moderate degree—is accompanied by resistance to one or both of the others, the most closely related pair being aureomycin and terramycin.

In the discussion of this subject in the Section of Pathology of the Royal Society of Medicine on February 5, a report of which appears on page 434, attention was concentrated on the mechanism of the change from sensitive to resistant. There are two clear examples in the clinical field where the process has evidently been one of strain selection. Sulphonamide-resistant gonococci and penicillin-resistant staphylococci are known or believed to have existed before these drugs were used, and they have naturally gained increasing predominance as sensitive strains have been eliminated. Studies of staphylococci have fortified this belief, since in this species natural resistance and artificially produced resistance to penicillin are of different natures, one depending on penicillinase formation, the other probably on a change in internal metabolism. But when resistance appears in a bacterial population which was previously wholly sensitive, as in a single given culture, either mutation or adaptation must have occurred. Which of these processes is in fact responsible has been a matter of violent controversy. As was pointed out at this meeting, it need not necessarily be assumed that the process is the same for all noxious agents or even for all antibiotics; the evidence in favour of the mutation hypothesis is far stronger in studies of streptomycin than in those of any other drug.

Of perhaps more practical interest is the property or behaviour of the bacterial cell on which resistance depends. At the R.S.M. meeting Gale pointed out that this may be of several different kinds. It may depend on the formation of something which neutralizes or destroys the drug in the environment, the clearest example of this being penicillinase. Resistance may also depend on impenetrability of the bacterial cell wall. Finally, and most often, it can depend on the establishment of an alternative metabolic pathway to one blocked by the drug. There may certainly be more than one of these points of interference with metabolism: the stepwise acquisition of resistance to sulphathiazole by staphylococci is an example of a change appearing to involve different stages of some metabolic process or perhaps actually different processes. Mitchison[1] has made the same suggestion about streptomycin resistance in tubercle bacilli. He found three distinct degrees of this among organisms in a single culture: one explanation of this could be that different concentrations affect either one, two, or three processes which the cell can successively by-pass. A similar assumption has been made by Eagle[2] to account for the "zone phenomenon" in the action of penicillin. It is well recognized that some bacteria, including *Strep. faecalis* and many strains of *Staph. pyogenes*, are killed at a maximum rate only by an optimum concentration, which may be quite low: above this the effect is retarded. Eagle's suggestion is that the optimum concentration acts at a late stage in some metabolic process, causing

1 *J. gen. Microbiol.*, 1951, **5**, 596.
2 *J. Bact.*, 1951, **62**, 663.
3 *Ann. Med. exp. Biol. fenn.*, 1951, **29**, Suppl. 1.
4 *J. Lab. clin. Med.*, 1951, **38**, 719.
5 *Bull. Johns Hopk. Hosp.*, 1951, **89**, 81.
6 *Antibiot. and Chemother.*, 1951, **1**, 472.

the accumulation of a toxic intermediate product, while high concentrations affect an earlier stage and thus prevent this product being formed. Although a good deal is known from the work of Gale himself and others of certain metabolic gymnastics imposed on bacteria by antibiotics, it does not follow that the effects so disclosed are the only ones caused, or are in fact those which are lethal to the normally sensitive cell.

Some speakers at the R.S.M. meeting also mentioned cross-resistance, a phenomenon which, as already mentioned, may sometimes deprive the three newer antibiotics of separate and successive usefulness (fortunately susceptibility to penicillin seems independent of that to any other drug). On the other hand, this is a relationship which seems to work both ways, because according to Kaipainen[3] and Gocke and Finland[4] habituation to streptomycin or neomycin may actually result in an increase in sensitivity to all three of the newer antibiotics. Still more remarkable and perhaps of clinical importance, although this remains to be proved, is the effect of habituation to aureomycin on a penicillin-resistant staphylococcus first observed by Chandler and his colleagues[5] and confirmed for this and two other penicillinase-forming organisms of different species by Monnier and Schoenbach.[6] These workers found that under the influence of aureomycin the organisms ceased to form penicillinase and consequently became sensitive to penicillin. There is much that remains to be explained in observations of this kind, but they may help in piecing together a more coherent view of the mode of action of antibiotics generally. It also seems that, if clinical practice can receive constant and detailed help from the laboratory in individual cases, many an otherwise difficult situation can be overcome. The use of combinations of drugs to prevent the acquisition of resistance to one of them is also a well-founded procedure in specified instances, although it may have unfortunate results if this fact encourages shotgun therapy.

THE SICKLE-CELL TRAIT

The curious tendency of the erythrocytes of some persons to become sickle-shaped has four principal aspects—biochemical, genetical, clinical, and anthropological—interrelated in such a complex manner that any investigation of one of them almost inevitably involves all the others. Of all Africans living south of the Sahara Desert, 15% at a rough estimate have in their red cells a haemoglobin molecule which is physico-chemically abnormal.[1] In the oxygenated condition the molecules are in solution inside the red cell like normal oxyhaemoglobin. In the deoxygenated state, however, their solubility is greatly reduced and the haemoglobin crystallizes out and distorts the cell into a crescentic or sickle shape. This change of form is readily observed microscopically and is the basis of the routine diagnosis of the condition. The change of form appears completely reversible, but it is possible that repeated changes may lead to haemolysis.

Sickling is inherited as a mendelian dominant: that is to say, inheritance from only one parent is sufficient to give rise to the condition in the offspring, and all who carry the sickling inheritance manifest it in their red cells. Some of them also suffer from a severe chronic anaemia, and the central medical problem is to ascertain why the remainder with sickling red cells apparently stay perfectly healthy. In the superficially similar Mediterranean (Cooley's) anaemia, in which a red-cell abnormality is also inherited as a mendelian dominant, heterozygotes suffer little or no disability, while homozygotes have a severe anaemia, usually fatal in early childhood. A similar view of the pathology of sickle-cell anaemia has tended to prevail in America, where the red-cell condition is present in only about 10% of negroes, implying about 0.5% of homozygotes. The hypothesis that the latter are all affected by anaemia has recently received strong support from the genetical work of Neel,[2] by whom it was originally put forward. Pauling and his colleagues[1] have moreover shown that all of the haemoglobin is abnormal in cases of anaemia but only part of it in sickling without anaemia.

In Africa, on the other hand, the frequency of sickling is over 20% in many populations, and reaches 45% in at least one. This implies a frequency of 1–6% of homozygotes. When other coincidental causes of anaemia are discounted in sickling individuals the frequency of true sickle-cell anaemia in Africa is certainly under 1% and probably very much lower than in America. Two main hypotheses have been put forward to explain this discrepancy. One is that under African conditions homozygotes nearly all die before or soon after birth. But it is almost inconceivable that the sickling frequencies found in some African populations could be maintained in face of such mortality. The other hypothesis is that the sickling gene causes anaemia only when inherited with another gene or genes derived from a European ancestor, which is likely to be much commoner among American than among African

[1] Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C., *Science*, 1949, 110, 543.
[2] *Blood*, 1951, 6, 389.
[3] *Amer. J. clin. Path.*, 1951, 21, 858.
[4] *Ann. Eugen.*, 1949, 14, 279.
[5] *Nature, Lond.*, 1949, 164, 494.

negroes. This problem will not be solved until further genetical studies have been carried out in Africa as well as in America. Singer,[3] in an admirable and scholarly review with a full bibliography, has recently surveyed the whole question.

The sickle-cell trait has hitherto been recognized only in Africans, in American negroes, in Yemenite Jews, in a small pocket of persons in Greece, and in a few scattered individuals of Mediterranean origin. It has thus been a reasonable assumption that sickling originated in Africa and that its occurrence elsewhere was evidence of African ancestry. In Africa its distribution has been the subject of numerous studies, but the only extensive ones which give full anthropological details are those of Beet[4] for Northern Rhodesia, and of Lehmann and Raper[5] for Uganda, and much remains to be done before the significance of this limited distribution can be seen. Two papers elsewhere in this issue report new facts about the distribution of the sickle-cell trait.

Drs. D. B. Jelliffe and J. Humphreys have examined 1,881 of the Yoruba of Nigeria. They found sickling in an overall frequency of 23.7%. In 51 infants under 2 weeks old sickling was absent, but no significant differences were found between the frequencies in the other age groups. There is thus no evidence for any differential mortality, as would be expected if the hypothesis were correct that all homozygotes suffer from sickle-cell anaemia, and that the rarity of this disease in Africa is due to the early death of affected individuals. To disprove this hypothesis completely, however, needs a statistical study of even larger numbers, or a detailed genetical study of numerous families. The absence of sickling in the youngest infants is explained by the authors as due to the persistence of the foetal type of haemoglobin to the exclusion of the sickling type. The article contains an admirable survey of the literature which, though shorter, will be more accessible than that of Singer to British readers.

The research of Dr. H. Lehmann and Miss M. Cutbush, on the other hand, was designed to test the hypothesis held by some anthropologists that the present population of most of tropical Africa contains an important component derived from Asia. This putative ancestry might be the source of one or both of the two most characteristic simple genetical characters of Africans, the sickle-cell trait and the Rh chromosome cDe, or R_o. Dr. Lehmann and Miss Cutbush have now found sickling in many members of three of the aboriginal tribes of Southern India. The overall frequency was 13%, but of the Irulas as many as 30% show the trait, a frequency higher than in most African populations so far tested. The cDe combination of Rh genes occurs in these Indian populations, however, with only a small fraction of the high frequency found throughout tropical Africa. Thus the sickle-cell trait cannot have been transmitted to Indians by a population genetically similar to modern Africans. Either it arose independently in the two areas, or, as is rather more probable on genetical grounds, it was inherited by the peoples of both areas from common non-African ancestors, with an Rh blood group composition different from that of present-day Africans though possibly like that of modern South Indians. This work thus provides results of great anthropological interest: medically it is important in adding yet another possible cause of chronic anaemia to the many known in India.

HABITUAL ABORTION

Attempts to determine the cause of habitual abortion, the condition in which consecutive abortions (usually three or more) occur without intervening pregnancies going beyond the 28th week, have so far been fruitless. Investigations on these patients in the non-pregnant intervals have brought to light little of contributory interest. Three possible groups of causes—paternal, maternal, and foetal—may exist. Some seminologists believe that seminal fluid containing many morphologically abnormal spermatozoa is likely to be responsible for abortion, but no one has shown that the husbands of women complaining of habitual abortion have characteristically abnormal semen. The possible maternal causes which have received most attention are vitamin deficiencies and hormonal inadequacies. Foetal causes include abnormalities of the ova and of the zygote not apparently due to abnormality of the maternal environment. The last two groups of causes deserve further comment.

The elegant studies of Hertig and Rock[1] on abnormal ova are very relevant to the question of foetal causes. From a series of 136 potentially pregnant women they recovered 28 early conceptuses. Twelve of these early ova were abnormal, and of these seven were certainly destined to abort. Four of the latter might not even have caused clinical signs of pregnancy because of their extreme abnormality. Yet in every case the endometrium showed normal secretory development. It was concluded that many spontaneous abortions could be attributed to foetal abnormalities, and that maternal causes were of minor importance.

The vitamin deficiencies which have been suggested as possible causes of abortion are those of C, K, and

E. Evidence on the implication of the first two of these has been presented by Javert and Stander[2] and by King.[3] Swyer[4] has pointed out that, whereas this evidence has not confirmed the existence of vitamin-C deficiency in aborting women, prothrombin deficiency was present in a significant number of cases. The literature on vitamin E is very extensive, and the value of this substance in the prevention of repeated abortion seems to have been both accepted and rejected in almost equally uncritical fashion. Some years ago Bacharach[5] reviewed the findings of Vogt-Möller[6 7 8] and of Watson and Tew[9] and compared their results with the findings of Malpas[10] on the likelihood of the successful completion of pregnancy after a series of previous abortions. Bacharach concluded that the chances of the differences between the published results of treatment in cases with two, three, and four previous abortions and the expected results with untreated cases being exceeded on the basis of random variation were 1 in 200, 1 in 10^{10}, and 1 in 10^{40}, respectively. Either the observations reported by the two groups of workers are fallacious or else there would appear to be strong evidence in favour of the therapeutic efficacy of vitamin E in habitual abortion—unless the outcome of pregnancy in untreated cases is generally more favourable than Malpas's figures suggest.

Hormonal inadequacies as maternal causes of habitual abortion have been conceived in terms of progesterone—and perhaps oestrogen—deficiency. No direct evidence of such deficiency appears to have been adduced, though a suggestion which would dispose of this objection is that a suddenly developing deficiency—such as before the placenta fully takes over the production of hormones from the corpus luteum—is the cause and not a persistently low secretion. At all events oestrogens have been claimed[11] to give 77% successful results in patients with habitual abortion, and progesterone by injection is very commonly administered to such patients, though evidence of its efficacy is lacking. The use of implants of progesterone seems to be a logical way of ensuring that the amount of hormone in the blood is kept steady, and is preferable to the erratic and evanescent effects of oily injections. In a recent paper in this *Journal* Drs. P. M. F. Bishop and N. A. Richards[12] published their further experiences with this treatment. In a combined series of 85 patients their success rate proved to be 85% in those women who had had two previous abortions and 72% in those who had had three or more. Compared with the expected success rates calculated by Malpas and of Eastman[13] these certainly represent a significant increase. It is, however, a little disturbing that vitamin E, oestrogens, and progesterone implants should all have the same success. The fact that Bevis[14] has obtained equally good results by investigation without treatment raises the question whether it is only the psychotherapeutic effect of all these various regimes that is responsible for the pregnancies going to term. Another doubtful point is that, though Malpas's and Eastman's figures may have applied to the populations they were studying, they may not, nevertheless, have universal validity. Indeed, if Eastman's calculation (shown in Table V in the paper by Bishop and Richards) is carried one step further, the spontaneous cure rate for women with four abortions should be 1%—which simply is not true. Bishop and Richards point out that the obvious way to settle the question whether a progesterone implant is endocrinologically or merely psychologically therapeutic is to treat alternate cases with implants of progesterone and an inert compound such as cholesterol. It would be even simpler to leave the alternate patients without any specific treatment, as Dr. D. C. A. Bevis implies in a letter published in this week's *Journal*, for it might then be found that the spontaneous cure rate is far higher than has generally been supposed.

1 *Amer. J. Obstet. Gynec.*, 1949, **58**, 968.
2 *Surg. Gynec. Obstet.*, 1943, **76**, 115.
3 Ibid., 1945, **80**, 139.
4 *Brit. J. Nutrit.*, 1949, **3**, 100.
5 *British Medical Journal*, 1940, **1**, 890.
6 *Lancet*, 1931, **2**, 182.
7 *Acta obstet. gynec. scand.*, 1933, **13**, 219.
8 *Klin. Wschr.*, 1936, **15**, 1883.
9 *Trans. Amer. Ass. Obstet. Gynec.*, 1935, **48**, 189.
10 *J. Obstet. Gynaec. Brit. Emp.*, 1938, **45**, 932.
11 Smith, O. W., *Amer. J. Obstet. Gynec.*, 1948, **56**, 821.
12 *British Medical Journal*, 1952, **1**, 244.
13 In J. V. Meigs and S. H. Sturgis's *Progress in Gynaecology*, 1947, p. 262, London.
14 *Lancet*, 1951, **2**, 207.

LOCATING BRAIN TUMOURS WITH ISOTOPES

In 1948 Moore and his co-workers found that the dye sodium di-iodofluorescein was substantially concentrated in brain tumours after intravenous injection.[1] After administration of this dye made with radioactive iodine a tumour in the brain could be discovered by the increased quantity of gamma radiation detected outside the intact skull. It was found possible to deduce the probable position of such a tumour within the brain by measuring the radiation at different points on the head's surface. The possible errors and pitfalls of this method of pre-operative diagnosis are many, but subsequent research by Moore, Selverstone,[2] and Ashkenazy in particular has (at least in the hands of these original workers) made the location of malignant gliomas very accurate.

Other substances which are concentrated in brain tumour tissue and have been used in large series of cases[3] are compounds of radioactive potassium (K^{42}) or phosphorus (P^{32}). Unlike radio-iodine, which emits long-range penetrating gamma rays, atoms of radioactive phosphorus give out β-particles which have a range

in the brain of only a few millimetres and are hence of value only in delineating the extent of a tumour when the cortex is exposed at operation. For this purpose a needle 2 or 3 mm. in diameter, with a Geiger–Müller counter near its tip, is used to probe the suspected area of the brain. As the needle reaches tumour tissue the counting rate of β-particles rises considerably, as judged by a rush of clicks in the headphones, so that the operator can obtain an idea of the depth and extent of the neoplasm, whereas naked-eye information may be quite inadequate. Radioactive potassium emits both gamma rays and β-particles, so that it should be possible to utilize it both before and during operation. However, there is little in the literature so far to indicate how successful this may be.

Attempts in Britain at confirming the American work on di-iodofluorescein have not met with great success. It is well to bear in mind how very exact any new method of location must be before it improves upon the well-tried techniques of ventriculography and arteriography. Loyal Davis[4] states that in his series of 340 patients investigated with di-iodofluorescein 95% accuracy was obtained, whereas "pneumography is 65% focally and 85% diffusely accurate." Many neurosurgeons and neuroradiologists in this country would, however, claim 95% accuracy by means of air-study and angiography. Radioactive potassium is unsuited to the location of tumours in the posterior fossa owing to the high counting rate obtained from the adjacent suboccipital muscles; location in this region has become extremely efficient by modern methods of encephalography and vertebral angiography.

There have, however, emerged several indisputable advantages to the patient and to the neurosurgeon. The use of these radioactive isotopes in the doses employed is without immediate harm to the patient, whereas contrast studies of the ventricles and the vascular tree may have very real dangers in subsequent complications. A patient whose condition demands investigation for the presence of a tumour even though such a diagnosis is considered unlikely can more readily and justifiably be subjected to a radio-isotope test than to a procedure having a known morbidity and mortality. The most impressive practical advance so far is the ability at operation to select a region in the brain giving a high count of β-particles after intravenous injection of radioactive potassium or phosphate ions. A biopsy can thus be obtained in the certainty that the pathologist will find a tumour within the small portion removed. Without this aid biopsy not infrequently fails owing to the difficulty at operation of distinguishing neoplastic tissue from neighbouring brain. Such an aid to diagnosis will, however, necessarily always be confined to those hospital centres which are suitably equipped and possess a physicist, since the handling of radioactive substances in bulk involves very special risks to the staff.

It is too early to assess this interesting work on radioactive isotopes in the central nervous system, yet it seems possible that, with the further development of more sensitive instruments and of substances having still greater differential affinity for neoplastic tissue in the skull, advances will be made in the treatment of brain tumours, particularly of the malignant glioma.

[1] *J. Neurosurg.*, 1948, **5**, 392.
[2] Selverstone, B., and White, J. C., *Ann. Surg.*, 1951, **134**, 387.
[3] —— Sweet, W. H., and Ireton, R. J., *Surgical Forum*, 1951, p. 371.
[4] Ibid., 1950, p. 357.

BACTERIAL PRODUCTS AGAINST CANCER

The clinical treatment of human tumours with bacterial products was introduced 75 years ago by Fehleisen, Bruns, Coley, and others. Coley used a preparation made from cultures of streptococci and of *Bacillus prodigiosus* which was called "Coley's mixed toxins." The Council on Pharmacy and Chemistry of the American Medical Association included this preparation in the list of remedies used for the treatment of cancer, although with some misgivings ("Its use in definitely inoperable cases may be quite justified, in many instances, as a desperate attempt to combat the inevitable"). This type of therapy was never widely used, for its successes were rare, and its administration was frequently followed by high temperature, nausea, and vomiting. However, interest in bacterial products as anti-cancer agents was renewed by the work of Gratia and Linz on animal tumours, and encouraged soon after by the experiments of Shear and Andervont on the separation of a polysaccharide inducing haemorrhage in tumours from broth cultures of *Bacillus coli*. The active fraction was extraordinarily potent, for 0.4 μg. of the polysaccharide induced haemorrhage in transplanted sarcomata in mice. Concentrates of the polysaccharide contained, after tryptic digestion, a small amount of firmly combined phospholipid, the removal of which destroyed the potency. Other kinds of mouse tumour reacted similarly; for example, spontaneous mammary carcinoma, the Ehrlich mouse carcinoma, and primary sarcoma induced with methylcholanthrene-choleic acid or with 3:4 benzpyrene. With filtrates from *Serratia marcescens* (*Bacillus prodigiosus*) the minimum dose required to induce haemorrhage in 50% of the tumours was found to be 0.1 μg. of the polysaccharide.

It was observed that mice bearing tumours were much more sensitive to the toxic effects of the agent than were normal mice. In one experiment a fifth of the dosage which just failed to kill normal mice was fatal for two-thirds of a series of mice bearing primary sarcomata. The changes in the tumours, haemorrhage and necrosis, appeared a few hours after injection of the polysaccharide. Complete and permanent regression of the induced tumour occasionally occurred, but usually some part of it survived and grew vigorously after most of the original growth had been destroyed. It soon became clear that the therapeutic dose was dangerously near the toxic dose, for apparently the breakdown of much tumour tissue released some highly toxic material. According to Shear,[1] "It thus appeared that the death of the tumor-bearing mice was largely ascribable not to the toxicity of the polysaccharide itself, but to some phenomenon resulting from the reaction of sensitive tumor tissue to the polysaccharide. The mice

[1] Shear, M. J., *J. Nat. Cancer Inst.*, 1944, **4**, 461.
[2] Brues, A. M., and Shear, M. J., ibid., 1944, **5**, 195.

with tumors exhibited symptoms resembling those of shock—namely, prostration, labored respiration, muscular atony, lowered body temperature, etc.; in tumor-bearing patients this agent produced a fall in blood pressure. . . ." Some clinical trials with the polysaccharide did not prove successful either.[2]

The chief exponent of polysaccharide therapy has thus to admit that this method is far from ideal. An immense amount of work has been devoted to chemotherapy in cancer, but of the thousands of compounds which have been tried out probably oestrogen for prostatic cancer represents to date the only success. There are now indications that this line of attack is losing some of its momentum, probably owing to a number of factors. For example, the screening of numerous compounds for tumour-inhibitory activity tends to become a collaboration between the synthetic organic chemist and the biologically trained technician, where the cancer investigator himself finds little intellectual stimulation. Secondly, the failure of so many potent tumour inhibitors to behave as practical anti-cancer drugs suggests that there is too close a similarity between neoplastic and normal cells for an agent to be able to destroy the one without seriously damaging the other.

Recent work on the role of dysgenic and environmental factors as causes of cancer suggests the possibility that the solution of at least some problems of cancer will come from quite a different direction—namely, by prevention instead of by treatment.

DIFFUSION RESPIRATION

Can respiration occur without respiratory movement? The question is again asked by Drs. Enghoff, Holmdahl, and Risholm, of Uppsala University, who describe in a recent paper[1] the establishment of "diffusion respiration" in man. This phenomenon was named by Draper and Whitehead,[2] who found from experiments on dogs that under certain conditions blood can be normally oxygenated by the lungs without respiratory movement and rhythmical changes in intrapulmonary pressure. They explain this by describing the action of the "haemoglobin-oxygen pump." During apnoea oxygen is removed from the alveolus by haemoglobin, but the normal elimination of carbon dioxide ceases. Carbon dioxide is retained in the blood and tissues, and the amount of oxygen leaving the alveolus during apnoea is therefore greater than the amount of carbon dioxide entering it. The pressure within the alveolus thus falls below that of the atmosphere, and movement inwards of the dead-space and atmospheric air occurs.

Three conditions must be fulfilled for this form of respiration to occur: the gas entering the glottis must be mostly pure oxygen, for if air is breathed nitrogen accumulates in the alveoli and quickly causes asphyxia; the airway must be perfectly free; the circulation must be adequate, as the capacity of the "pump" is proportional to the volume of reduced haemoglobin flowing through the alveolar capillaries. Diffusion respiration has been found effective in animals for 30 minutes; but after this the oxygen content of the blood falls, probably because of the Bohr effect—a consequence of the action of CO_2, with respiratory acidosis and low blood *p*H.

Enghoff and his co-workers induced apnoea in the human with an intravenous barbiturate and curare. A cuffed endotracheal tube was first passed under general anaesthesia, and the patient was allowed to breathe oxygen from an anaesthetic machine for 10 minutes. The tracheal tube was then connected to a spirometer containing oxygen, which operated without exerting measurable positive pressure. Apnoea was maintained for about 5 minutes, the maximum being 7 minutes 20 seconds. The oxygen consumption during this period was the same as during the time when respiratory movements were still taking place. At the end of the period of apnoea the blood oxygen had not fallen, but the carbon dioxide had increased; no changes were noticed in the functioning of the heart and circulation.

The mechanism of diffusion respiration must not be confused with the insufflation process which was first described by Hook[3] in 1667 and was introduced into anaesthesia by Barthelemy and Dufour[4] and Meltzer and Auer[5] in the first decade of this century. These workers kept the lungs distended by gases under pressure; in diffusion respiration no pressure is applied, and apnoea is a result of respiratory paralysis. Meltzer and Auer shortly afterwards admitted their technique to be unsatisfactory, which was generally agreed by their contemporaries. Moreover, they do not appear to have maintained distension of the lungs but interrupted the pressure intermittently, so turning their method into one of artificial respiration. Diffusion respiration is more like the phenomenon described a little earlier by Volhard[7] and Hirsch,[6] who experimented to discover if ventilation of the trachea would be sufficient to allow adequate respiration to take place. Oxygen at a low pressure was administered through one-half of a double endotracheal cannula, and the animal's respiration stopped with curare; they found that if respiratory movement was restored within an hour the animal recovered, but after longer periods it died. If the oxygen was replaced by air death occurred rapidly.

The oxygen content of the blood was maintained during Volhard's experiments, but the content of carbon dioxide was trebled and death occurred from carbon dioxide poisoning. This observation has achieved a new importance since curare has been used in the operating theatre as freely as in Volhard's laboratory, and the anaesthetist's technique of artificial or assisted respiration has as its object the efficient removal of carbon dioxide as much as the supply of oxygen. Diffusion respiration is a physiological freak which appears to have no clinical application; whether it occurs at all is questioned by Conroe and Dripps,[8] who suggest that the alveoli are not stationary but oscillated by cardiac movement.

1 *Nature, Lond.*, 1951, **168**, 830.
2 *Cur. Res. Anesth.* 1949, **28**, 307.
3 *Phil. Trans. Roy. Soc.*, 1667, **2**, 539.
4 *Pr. méd.*, 1907, **15**, 475.
5 *J. exp. Med.*, 1909, **11**, 622.
6 *Über die künstliche Atmung durch Ventilation der Trachea*, 1905, Giessen.
7 *Münch. med. Wschr.*, 1908, **55**, 209.
8 *Annu. Rev. Physiol.*, 1945, **7**, 653.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

ANAESTHESIA FOR MINOR PROCEDURES

BY

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For most minor operations the anaesthetic is also of a minor character. As such it should be characterized by a high degree of safety, simple equipment and method of administration, pleasant sensation and memories to the patient, speedy recovery, and, not least, effectiveness for the surgeon. The occasional anaesthetist, however, must not be misled into thinking that, because the proposed surgical procedure is a minor one, the anaesthetic for it will for a certainty present no difficulty or that little skill will be required. Many examples of the reverse come to mind. The patient with submaxillary cellulitis may need but a small incision, but, as is well known, he may well die before the surgeon even starts his little operation. The child who is to have a small cut sutured may regurgitate a piece of the apple he was eating when he fell down and cut himself, and die of acute respiratory obstruction therefrom. The much tattooed, burly seaman who is to have an easy dental extraction may be in the chair for only a few minutes, yet his short stay may not only leave its mark both on the dentist's furniture and on the anaesthetist's reputation, but the momentary anaesthesia required may have been obtained only at the cost of extreme and dangerous anoxia. These examples are given here, not to frighten the general practitioner, but to put him on his mettle and to forewarn him never to relax his awareness of possible, though happily rare, difficulties and dangers.

Children

Examples of common minor operations in children for which the practitioner is likely to be asked to give an anaesthetic are circumcision, tonsillectomy, the setting of a greenstick or other fracture, and the opening of an abscess. Before any such anaesthetic a hypodermic injection of atropine should always be given. Up to the age of 2 years a suitable dose is 1/200 gr. (0.32 mg.); from 2 to 5 years, 1/150 gr. (0.44 mg.); and from then onwards 1/100 gr. (0.65 mg.)—all these being given about half to one hour before the operation. In the case of children over 2 or 3 years old, ½ to 1 gr. (32 to 65 mg.) of pentobarbitone sodium by mouth two hours beforehand will make the child placid or even sleepy and fear and crying will be largely obviated.

For the anaesthetic itself many drugs and techniques are available, but for young children and infants the best method of all for the practitioner, as indeed it is for the specialist, is an induction with either ethyl chloride or vinyl ether, followed by ether dropped on to a gauze mask. The ethyl chloride should be administered cautiously, squirt by squirt, but only until the child ceases to struggle, for its purpose is not so much to produce full anaesthesia as to subdue the child and to depress its reflexes enough for it to breathe without restraint the more irritant ether vapour. The addition of ether to the mask is then started. Should insufficient ethyl chloride have been given and the child respond to the ether by breath-holding, coughing, or swallowing, a little more ethyl chloride can be given. By this means overdosage with ethyl chloride is avoided. It is rarely necessary to use gamgee between the mask and the face; certainly this should not be done in the hope of avoiding an "anaesthetic eye," for this condition, though it may possibly be caused by the anaesthetic coming in contact with the cornea, is more commonly the result of rubbing the cornea with gauze or a towel. Oil should not be put into the eye before or during an anaesthetic, because any ether in the vicinity will surely dissolve in the oil.

For children over the age of about 7 or 8 years nitrous oxide, oxygen, and a little ether may be administered from a Boyle apparatus in the manner described for adults, although even for these older children open drop-ether anaesthesia is most effective and very suitable.

After an operation lasting a few minutes recovery from ether anaesthesia of this sort is very rapid and, apart from perhaps an occasional single vomit, the child is none the worse. It may be put to sleep in its mother's arms or even sitting up on a chair or on the operating table if the anaesthetist thinks it will be kinder. As soon as the child is under, it should be placed on an operating table so that its airway may be properly controlled and the anaesthetic administered. An artificial airway is generally unnecessary in infants and children and should on the whole be avoided as more likely to be traumatic than helpful. Respiratory obstruction is more often due to the anaesthetist's fingers holding up the infant's lower jaw than to leaving it alone.

When the operation is over the child should be placed on its side and carefully watched until consciousness returns, so that respiratory obstruction or vomiting can be dealt with. A good guide in this respect is not to let the child go back to the mother until it has recovered enough to cry.

Adults

Common examples of minor procedures are incision of septic finger or abscess, the setting of a minor fracture, biopsy, and removal of an ingrowing toe-nail. As the patient is likely to be ambulant and will want to return to that state as soon as possible after the operation, premedication of any sort is best avoided. In very nervous patients this view may be relaxed somewhat, but even two or three aspirin or codeine compound tablets half an hour before the operation, or a ½-gr. (32-mg.) capsule of pentobarbitone sodium one hour before, will have the right effect without interfering very much with the patient's rapid recovery after the operation, apart from the need to refrain from driving home in a car.

The most suitable anaesthetic for these little operations is nitrous oxide and oxygen, with, if necessary, a trace of trichlorethylene added to the gases before the operation starts. The induction of anaesthesia should not be hurried; it is a common but erroneous belief that nitrous oxide anaesthesia is a quick method. The more slowly induction is carried out the smoother will the subsequent anaesthesia be. Induction is started with pure nitrous oxide and after a few breaths oxygen is added in gradually increasing amounts till, finally, a mixture of about 1.5 litres a minute of oxygen and about 7 litres a minute of nitrous oxide is being given. An average time for induction is 7 to 10 minutes. The trichlorethylene, when it is to be used, should be added cautiously to the gas mixture soon after the start, and as soon as the patient is breathing regularly it should be turned off. Poor anaesthesia is more often due to insufficient oxygen than to too much. The patient's colour should in general be a bright crimson and in any case never worse

than a slightly dull pink. Any obvious cyanosis indicates that more oxygen should be added to the mixture. It is better to use a little trichlorethylene than to cut down the oxygen.

Elderly People

With old people, and indeed with ill and feeble patients in general, particular care should be taken that at no time is the oxygen supply inadequate. The patient's ears should remain crimson the whole time. In these patients more than in any other is it preferable to add a little trichlorethylene to the gas and oxygen than to run the real risks of insufficient oxygenation.

Dental Extractions

These patients form a group in themselves. In young children ethyl chloride or vinyl ether on an open mask is suitable, while for older children nasal nitrous oxide and oxygen may be used, the anaesthetist erring on the side of too much oxygen rather than the reverse. In adults, nasal nitrous oxide and oxygen from an apparatus such as the Walton or McKesson is the routine everywhere. These machines allow slight positive pressure to be used and permit the oxygen percentage to be varied easily without upsetting the pressure. The technique of continuous nasal nitrous oxide is soon learned. The secrets for success are a proper position of the patient in the chair, in which the head is in a natural relation to the body, being neither extended nor flexed; an unhurried induction; satisfactory insertion of a gauze mouth-pack so that debris is held without the respiration being obstructed; the use of slight positive pressure; and adequate support by the anaesthetist of the patient's head and jaw during the extraction.

Thiopentone

This substance is extremely valuable for putting a patient to sleep in a pleasant manner. Its use as the sole anaesthetic, however, should be attended with the greatest of caution. Many fatalities and near fatalities have occurred because the anaesthetist has failed to realize that this drug, while having marked hypnotic properties, is a poor analgesic, and that it will not prevent reflex movement to pain until enough of the drug has been administered to practically stop breathing.

In practice a 5% solution is made up and injected through a fine needle very slowly, allowing plenty of time for the drug to circulate, until the patient is unconscious. For the average fit adult this dose will be about 0.25 g. (5 ml. of 5% solution). Great care is taken that the injection is into a vein and not into the tissues or into an artery. In the former instance the swelling outside the vein is usually obvious, while the patient complains of pain at the site of injection. In the latter the most constant symptom is severe pain of a burning character in the hand. The dire results of intra-arterial injection make it imperative to avoid any veins which lie contiguous to an artery or in a position where an aberrant artery is likely to be found.

Once the patient is asleep the injection should be stopped and the anaesthetic continued with nitrous oxide and oxygen, with or without trichlorethylene. If it is the wish of the anaesthetist to use thiopentone as the sole anaesthetic, the patient's reaction to pain should be tested as soon as he is unconscious. For example, the surgeon might prick the skin with his knife. If necessary another small amount should be given and the patient tested again. This manœuvre is repeated until no movement takes place. The habit of arbitrarily deciding on what the single dose is to be, and then injecting, is to be condemned, because in this way overdosage easily occurs. The reaction of patients to thiopentone varies widely and it is nearly impossible to judge this merely by looking at them beforehand. It is almost certain that respiration will be very depressed or even absent at the moment that the patient no longer reacts to the operation. When he is robust and the dose of thiopentone correct, respiratory activity quickly recovers spontaneously. If breathing does not start or regain its vigour within a minute or so the anaesthetist should not hesitate to resort to artificial respiration, by squeezing the chest, or better still by a squeeze of the reservoir bag, or by blowing with the lips down a facemask held on to the patient's face so that his lungs are inflated. Recovery after thiopentone is markedly slower than after nitrous oxide and a period of drunkenness may persist for some hours.

Though no more apparatus than a syringe and needle is required, the less obvious but more important ingredients for safety with thiopentone are caution and long experience. The practitioner will have less anxiety and have better success with his minor anaesthetics if his first inclination is towards inhalation anaesthesia rather than intravenous for any but the most minor of minor procedures.

Difficulties

Respiratory Obstruction—The practitioner should beware of anaesthetizing patients with marked respiratory obstruction. These patients may die very quickly as soon as they are made unconscious and unable to use the accessory muscles of respiration on which perhaps their life was depending. These cases, though the surgery may be small in extent, call for the greatest skill and experience on the part of the anaesthetist. Little more will be said about them here, except that the essence of safety is to relieve the respiratory obstruction before the patient is made unconscious.

Vomiting.—If the patient is known to have had food within three hours of the anaesthetic it is better to postpone the operation rather than to risk the very grave dangers of regurgitation and inhalation of vomit. Many patients die each year from this cause, although they were having a simple anaesthetic for a minor operation. In cases of emergency it is justifiable to empty the stomach by passing a large stomach tube just before the anaesthetic is begun. The gravity and danger of inhaling vomit cannot be overemphasized, as also the fact that this may occur with the most trivial procedures. In these instances the tragedy is all the greater.

Resistance to Anaesthesia.—The practitioner may find that patients who are excitable, in great pain, addicted to alcohol, or generally robust may be difficult to subdue enough to remain immobile during the operation. When this occurs he should not hesitate to add trichlorethylene to the nitrous oxide and oxygen and allow plenty of time for this drug to take effect. If this difficulty is anticipated, because of reports of previous anaesthetics from colleagues or the patient himself, premedication such as that mentioned above should be ordered; when this is impracticable an intravenous injection of 10 to 15 mg. of pethidine may be given just before the anaesthetic is started.

Fire and Explosion

The practitioner should bear in mind that both ether and ethyl chloride are highly inflammable substances. They should never be administered in the presence of an open flame of any sort or of any other obvious source of ignition. Smoking in particular should never be allowed in the vicinity of an anaesthetic. The addition of oxygen to either of these substances makes them highly explosive, and if such a mixture is ignited a violent detonation may occur, with grave injury to the patient and perhaps structural damage to the room. Whenever a diathermy is to be used or the anaesthetic is to be administered in the presence of an open flame, nitrous oxide alone or with some trichlorethylene, or thiopentone, should be the anaesthetic selected. Chloroform cannot easily be justified except in unusual circumstances for a minor operation, in view of the availability of the alternatives mentioned and of the known dangers of cardiac arrest, of overdosage, and of late poisoning, the incidence and occurrence of all of which are now established beyond reasonable doubt.

Post-operative Care

The patient should be allowed to recover from his short anaesthetic in his own time and no attempt made to waken him by slapping his face or other manœuvre. Even after consciousness has returned, enough time should be allowed for him to feel really recovered before he gets to his feet. On no account should a patient be allowed to drive a car after an anaesthetic, or even to go out into the street unless accompanied by another adult. Although apparently normal, a period of post-operative mild drunkenness and disordered judgment may persist for some hours, particularly if more than the smallest amounts of trichlorethylene or thiopentone have been used.

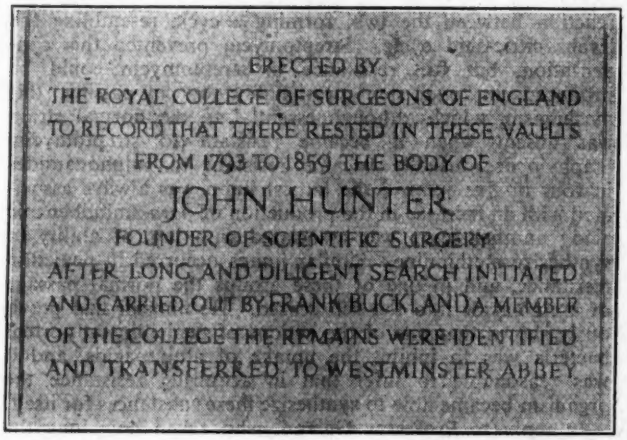
"THE FOUNDER OF SCIENTIFIC SURGERY"

HUNTER MEMORIAL AT ST. MARTIN'S

The President and members of Council of the Royal College of Surgeons, with members of the Hunterian Society and others, attended at St. Martin-in-the-Fields on February 14 when a tablet in the crypt was unveiled and dedicated recording the fact that the body of John Hunter had rested in the vaults of that church from 1793 to 1859, when it was removed to Westminster Abbey. After the General Thanksgiving and prayers the President of the College (Sir Cecil Wakeley) read a lesson from the Wisdom of Solomon:

"For God himself gave me an unerring knowledge of the things that are, to know the constitution of the world, and the operation of the elements . . . the natures of living creatures and the ragings of wild beasts, the violences of spirits and the thoughts of men, the diversities of plants and the virtues of roots: all things that are either secret or manifest I learned, for she that is the artificer of all things taught me, even wisdom."

The clergy and a part of the congregation then proceeded to the crypt, where Sir Henry Dale unveiled the tablet, which was dedicated by the Dean of Westminster. When they


ERECTED BY
THE ROYAL COLLEGE OF SURGEONS OF ENGLAND
TO RECORD THAT THERE RESTED IN THESE VAULTS
FROM 1793 TO 1859 THE BODY OF
JOHN HUNTER
FOUNDER OF SCIENTIFIC SURGERY
AFTER LONG AND DILIGENT SEARCH INITIATED
AND CARRIED OUT BY FRANK BUCKLAND A MEMBER
OF THE COLLEGE THE REMAINS WERE IDENTIFIED
AND TRANSFERRED TO WESTMINSTER ABBEY

had returned to the church a commemorative address was given by Sir Gordon Gordon-Taylor, who narrated briefly the circumstances attending the discovery and identification of John Hunter's remains.

Identification of Hunter's Coffin

At a Hunterian dinner in 1847 Dean Buckland of Westminster, father of Frank Buckland, expressed regret that the medical profession had erected no monument to Hunter, and mentioned that he had himself suggested the propriety of such a monument in Westminster Abbey. Eleven years later Frank Buckland, then an assistant surgeon in the Second Life Guards, read an Order in Council requiring the vaults of St. Martin's to be cleared of their coffins, and, having confirmed the fact of Hunter's burial there, he set himself the macabre task of finding Hunter's coffin among more than 3,000 in the charnel house. It was the last but one exposed to view, and a few weeks later, in a gathering of more than 600 persons, the remains were reinterred in the Abbey between the graves of Ben Jonson and Charles Lyell. Words written by J. F. South, then Junior Vice-President of the Royal College, and contained in the ornamental brass which covered Hunter's remains in the Abbey, doubtless mirrored the views of surgeons nearly 70 years after his death:

"A gifted interpreter of the divine power and wisdom at work in the laws of organic life . . . the founder of scientific surgery."

To this day they saluted one "who was great through mortal days and died of fame unshorn."

After this homage to the great shade of Hunter, Sir Gordon Gordon-Taylor proceeded to speak of Frank Buckland, whom the tablet also commemorated, describing him as a somewhat erratic surgeon-anatomist, a great investigator in natural history, with a bias for turning to practical use the facts he ascertained, and, like Hunter, a great collector. He formed a fish collection which he left to the Science Museum, South Kensington, and his work was continued by the Buckland Research Foundation in gathering together and summarizing knowledge, especially recently acquired knowledge relating to important food fish.

A third name, he added, inevitably stole into the thoughts of some of them, for it was owing to the zeal and enthusiasm of the late George Grey Turner that the project to place the plaque in the church had come to fruition. With many a difference between them, Hunter, Buckland, and Grey Turner were all great collectors and fervent believers in the value of the museum; all three were incessantly industrious, and all died immersed in the work they loved. Their name and life and work would endure long after any memorial in stone had perished. In the great words which Thucydides put in the lips of Pericles in his famous funeral oration over the Athenian dead: "The whole earth is the tomb of great men. Neither is their name graven only on stone which covers their clay, but abideth everywhere without visible symbol, wrought in the stuff of other men's lives."

Nova et Vetera

AN ANCIENT MEDICAL COMPENDIUM

Caelius Aurelianus: On Acute Diseases and on Chronic Diseases. Edited and translated by I. E. Drabkin. (Pp. 1,019. £5 12s. 6d.) Chicago: University of Chicago Press. London: Cambridge University Press. 1951.

One of the most versatile of the ancient Greek physicians was Soranus of Ephesus, who flourished about 100 A.D. He wrote on almost every aspect of medical theory and practice, as well as on philosophical and other subjects. Most of his works have disappeared. His gynaecology, however, survives in some very peculiar, very early, and very famous illustrated manuscripts, the influence of which persisted for fifteen hundred years and may still be traced. Of his other writings by far the largest and most complete, though lost in the original Greek, has come down to us in a Latin version prepared in the fifth century by one Caelius Aurelianus of Numidia, the modern Morocco. This work is an immense treatise in two parts, one on acute and the other on chronic diseases. The manuscripts of this Latin translation have also been lost, so that the modern editor must rely on editions of the sixteenth century, making such emendations as his skill in scientific literary criticism will permit. Such an edition has hardly been attempted since 1709, so that Professor Drabkin has, in effect, been working in a new field, hitherto almost untouched by modern scholarship. An edition of Caelius Aurelianus has long been regarded as a special need of Latin scholarship, for it has points of linguistic as well as of medical interest.

In the later pre-Christian and the earlier Christian centuries medical thought developed into various sects or "schools" founded on different philosophic principles. The most prominent, and for long the most influential, of these was the so-called "Methodist," to which Soranus and his

translator adhered. The origin and development of this school is briefly treated by Dr. Drabkin. We could wish that he had given far more space to a general discussion of these schools. The dominant philosophical element of the Methodist school was scepticism, but this attitude was sufficiently moderate to permit the formulation of certain principles, based on observation of individual cases. The doctrine of the Methodists was basically atomic. They held that the atoms moved about freely in "pores" in the bodily fabric. Disease was supposed by them to consist in changes in the pores, which were either abnormally stringent and narrow or, on the other hand, excessively relaxed. The Methodists repudiated the doctrine of the "Dogmatic" school that perversion or misplacement of the humours was the cause of disease—a doctrine which survived almost intact into the nineteenth century, had some place even in quite modern medicine, and has left its impress on current medical nomenclature. The work before us is the main source of our knowledge of the opposing Methodist school. Hence its historical importance.

The enormous text of Caelius Aurelianus, together with the excellent English translation that confronts it, occupies no fewer than a thousand pages of Dr. Drabkin's impressive volume. It would be impossible here even to sketch the contents. As knowledge is at present distributed, it must be regarded as an undertaking made for the sake of the small band of medico-historical specialists, but for them it is indispensable. It must suffice here to say that the presentation and scholarship displayed are all that could be desired. The work will become a *locus classicus* for all interested in ancient medicine, who will find it specially useful in tracing the origin and descent of medical terms. Professor Drabkin is to be both congratulated and thanked for his disinterested labours in adding an important reference book to the scholar's library. Only great foundations for learning, such as the Carnegie, the Guggenheim, or the Bollingen Foundation, who have supported this work, could have met the expense necessary for its beautiful production. Those responsible for these funds will have the satisfaction of having subsidized a permanent addition to learning, for which the writer of this review is himself personally grateful.

CHARLES SINGER.

Reports of Societies

DRUG RESISTANCE

A meeting of the Pathology Section of the Royal Society of Medicine was held at 1, Wimpole Street on February 5, when "The Drug Resistance of Micro-organisms" was the subject for discussion.

Professor L. P. GARROD opened the discussion with a survey of the subject. Resistance to drugs, first observed in trypanosomes, and now a most important problem in connexion with bacteria, was not confined to micro-organisms; it could be observed in populations of insects to agents such as dichlor-diphenyl-trichlorethane (D.D.T.) or even in human beings to narcotics. Such resistance was most commonly developed to drugs having a highly selective and subtle type of action, but some degree of resistance could be developed against even general protoplasmic poisons such as phenol. Penicillin resistance was seldom a problem except with staphylococci. Sulphonamide resistance was very often observed. Streptomycin resistance was very frequent and rapid in its development; it could reach a point where organisms were dependent on the drug for their continued growth. Cross-resistance occurred occasionally, particularly to the antibiotics most recently extracted from streptomyces; strains of bacteria that had developed resistance to "aureomycin" were usually also resistant to "terramycin" and vice versa, and they were sometimes slightly resistant to chloramphenicol. Gram-negative bacilli were the worst offenders: the pyogenic cocci had much less capacity to become resistant to the newer antibiotics. There was some evidence that when penicillinase-forming species acquired resistance to aureomycin they became more sensitive to penicillin, and in other cases "neomycin" treatment could in some way decrease resistance to aureomycin and terramycin.

Mechanism of Resistance

It was interesting to speculate on the possible mechanisms by which resistance could be acquired. There was evidence that organisms having innate drug resistance could become prevalent by strain selection: variations in sulphonamide sensitivity existed among strains of gonococci isolated before 1937 that could never have come into contact with the drug. In most instances the change occurred in a bacterial population which had previously been wholly sensitive. Whether such change in resistance was the result of cell adaptation or of mutation was a subject on which there had been much argument, and the issue had not been made clearer by the introduction of genetical dogma which was probably irrelevant when one was considering cells dividing by binary fission, since the daughter cells might be expected to have all the parental characteristics, whether hereditary or acquired.

Dr. E. F. GALE continued the discussion from the experimental point of view. The usual technique by which resistant organisms were produced and studied was by growing them in serial dilutions of the drug and selecting for further culture organisms that just survived the highest concentration. Usually resistance appeared in a series of jumps or steps, but occasionally complete resistance appeared in one step. Two such instances had been investigated: in the first, organisms had acquired complete resistance to penicillin in one step by developing an enzyme, penicillinase, which destroyed the drug before it ever came into contact with the organism; in the second, W. W. Umbreit had demonstrated a mechanism in bacteria whereby addition of oxaloacetic acid increased the ability of the organism to oxidize pyruvic acid; he ascribed this to a condensation reaction between the two, forming a cycle resembling the Krebs citric-acid cycle. Streptomycin prevented this condensation, but full resistance to streptomycin could be produced in one step presumably by by-passing this mechanism, which although essential to the normal strain was absent when it became resistant to streptomycin. Staphylococci usually became resistant to sulphonamides in four or five jumps; the largest jump was always associated with an increase in the production of *para*-aminobenzoic acid; another jump was associated with loss of ability to synthesize methionine. Similar jumps occurred in penicillin resistance, and in one of these groups the normal passage of amino-acids into the cell ceased. He himself had previously shown that one of the actions of penicillin on normal bacteria was to inhibit the uptake of amino-acids, and it was reasonable to infer that in acquiring resistance the organism became able to synthesize these substances for itself.

In reply to Professor Garrod, who asked how long the interruption of a metabolic process would take to kill a bacterial cell, Dr. Gale replied that studies with isotopes showed that ammonia nitrogen could become incorporated in the cell in as little as three minutes; if a process such as this were interrupted cell death would probably occur in a matter of minutes.

Effect of Bacterial Environment on Development of Resistance

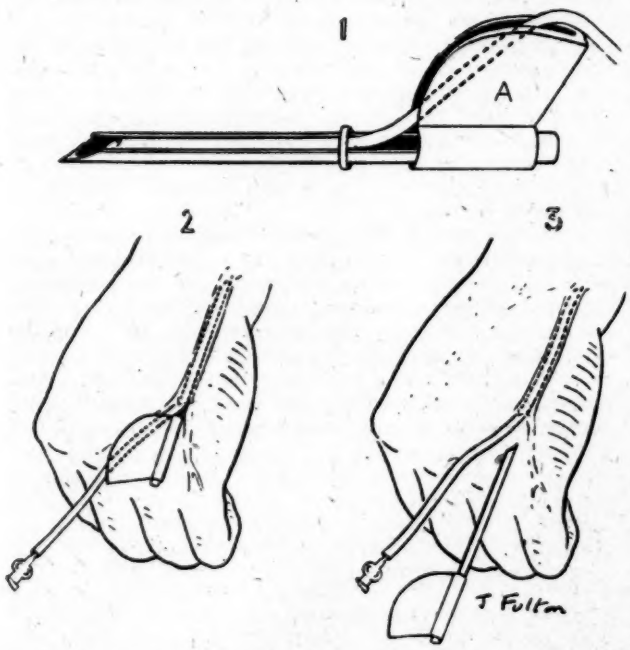
Professor R. KNOX emphasized that in considering the resistance of micro-organisms to drugs or antibiotics it was necessary to distinguish clearly between enzyme adaptation and natural selection. He suggested that often a resistant mutant in a bacterial population might be selected out only if growth conditions were such that it could adaptively produce an essential enzyme. As an example, he quoted some work he and Dr. P. Collard were doing with a penicillinase-producing strain of *B. cereus*. In the absence of penicillin, the organism grew well in broth at 37° and 42° C. When grown at 37° C. in the presence of penicillin,

the organism appeared to be highly resistant. This resistance depended on its power to produce penicillinase. At 42° C. the organism was 10–100 times more sensitive, presumably because it could not adaptively produce penicillinase at that temperature. This example also showed the need for standardizing the conditions of growth in assessing the sensitivity of micro-organisms.

Preparations and Appliances

AN INTRODUCER FOR PLASTIC CANNULAE

Dr. J. V. MITCHELL, of the Nuffield Department of Anaesthetics, Oxford, writes: The advantage of using fine plastic tubing as an intravenous cannula is often lost through the difficulty experienced in its insertion. The introducer described here, however, allows tubing to be inserted as easily and as aseptically as an intravenous needle of a size similar to the selected tubing. It is prepared from the smallest aspirating needle which will admit the tubing into its lumen. For two-thirds of its length part of the wall is removed by grinding, leaving a U-shaped section bearing the point (Fig. 1). The needle mount is removed, being replaced by a holder (Fig. 1, A), which helps to control the shaft during introduction. The holder is slotted to prevent contamination of the tubing by the fingers. The end of the tubing is bevelled in the same plane as the point of the needle, near which it lies in the groove. A minute rubber ring holds the tubing in place during sterilization. An intravenous drip can be attached to the other end of the tubing, or a Gordh diaphragm on a needle, if intermittent injections are intended.



The bore of the tubing is increased to such a slight degree by the introducer that a vein on the dorsum of the hand is generally found convenient for the smallest size of tubing. The wrist is constricted and the vein further dilated by a flick of the finger. The skin is sterilized, and the shaft with the tubing in place is inserted into the vein (Fig. 2); the constriction is released and the tubing advanced into the vein. The introducer is then withdrawn (Fig. 3). A small dressing with strapping is applied to fix the tube in place. The largest polythene tubing has been inserted with equal ease into a suitable vein in the forearm.

My thanks are due to Mr. Richard Salt, of the Nuffield Department of Anaesthetics, who made the introducer for me.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

What Doctors Prescribe

SIR,—I have read with great interest the article by Professor D. M. Dunlop and colleagues on a survey of some prescriptions issued on Form E.C.10 during 1949 (February 9, p. 292) and also recent correspondence on prescribing habits and on changes in doctor–patient relationship. The following summary of a pilot investigation made last year seems to me to indicate the sort of information which is required in order to answer some of the questions which are being asked. I suggest that an extension of such studies is required and might well be organized on a wide scale.

The practice selected was a mixed industrial and country one in South Wales, worked by one man, the period five weeks in summer. A note was made after surgery of every relevant detail, copied from the N.H.S. record cards and supplemented while memory was fresh. Analysis of such records (my part of the task) can give only a glimpse of one part of one man's practice, but several interesting points emerge. From a list of approximately 2,800 patients no fewer than 640 (23%) consulted him during this "quiet" tenth of the year, making 976 visits to the surgery (average number of visits 1.72, duration six minutes) and being seen in their homes 129 times (average number of visits 1.8). Of these 976 consultations no fewer than 119 (12%) were made by proxy, and 34 in all (3.5%) were, after cool consideration, noted as unsatisfactory in that the patient had a contempt for the doctor rather than a desire for his help. The age and sex distribution of the patients was a close reflection of the local population distributions. Of the 640 patients 423 (66%) were considered to have something the matter with them physically and 68 (13.5%) mentally. Only 41 (6.4%) were sent to bed, 44 (6.9%) to outpatient departments, and 81 (12.6%) given treatment in the surgery. A partial or complete examination was made on 365 patients (64% of those visiting the surgery) and on all bed patients.

The pattern, therefore, is of steady, careful, time-consuming work additionally burdened by record-keeping, telephone, etc., and relieved by the daily round of visits. In winter the burden must be severe.

As to the prescriptions, 570 of these were issued (89% of patients), of which 489 (86%) were from the *N.F.*, 77 (13.4%) were proprietaries, and only four (0.7%) were "classical" scripts written by the doctor. This figure casts doubt, not on the capability of the physician to write a prescription, but on the need to devote much time to teaching the medical student how to write prescriptions. The number of proprietaries ordered would have been much less if the 1952 addendum to the *B.P.* 1948 had been official at that time (antihistamines). No fewer than 441 (78%) were for "bottles"—stomachics, cough mixtures, tonics, and liniments. Analysis of the scripts on the same lines as those in the article quoted gives the following results: tablets 33%, mixtures 30%, skin 10.6%, dressings 8.9%, liniments 5%, powders 3.9%, guttae and E.N.T. prescriptions 3.8%, and injections 2%. The greater proportion of powders recorded here than in the wider survey indicates the preference of the individual for pulv. trisilicas co. whenever possible, in face of some consumer resistance. The number of liniments (mostly terebinthinae) is indicative of local climate, housing, and employment (fibrositis and bruises). Of all *drugs* prescribed the frequency distribution of the main items was as follows: cough (mainly linctus codeinae) 18.8%, stomachic 13.2%, hypnotic (almost all barbiturate, a few chloral and bromide) 13%, antipyretic analgesics 6.6%, antihistaminics (half topical) 6.2%, tonics (nux vomica) 4.4%, spasmolytic, etc. (ephedrine) 3.4%, sulphonamide (half gutt. sulphacetamid. mit.) 3%, penicillin (half topical) 2.4%, cardiac 2.4% (no tincture of digitalis), analgesics 2.2%, iron, laxatives, and hormones (stilboestrol) 2% each, urinary 1.6%, amphetamine (slimming) and vitamins (C and D) 1.4% each.

Several points are worthy of comment. The high percentage of cough mixtures and of spasmolytics (ephedrine and isoprenaline for asthma) is indicative of mining practice. Isoprenaline inhalation is much preferred to adrenaline by injection and is often as effective. Tonics were still needed

in summer and were often demanded. Antihistaminics are being prescribed with great frequency for skin diseases. This phase will pass. Pethidine was preferred to morphine for many cases: amidone was not so successful. The relative infrequency of prescribing penicillin was partly due to lack of clear indications for the need of parenteral treatment in patients not sent to hospital and partly due to the technical trouble of such administrations. The infrequency of prescribing iron was due to the lack of clear indications for its use in the absence of a haemoglobinometer. How many practitioners use their haemoglobinometer regularly?—I am, etc.,

Department of Pharmacology,
Welsh National School of Medicine,
Cardiff.

J. D. P. GRAHAM.

SIR,—An F.R.C.P. from a department of therapeutics writing about general practice is rather like a naval gunnery expert from Hayling Island giving directions about the trawling of herrings: he knows a vast amount about nautical affairs, but perhaps has no actual experience of the matter in hand. And, although he is able to make many shrewd observations, his article must be salted with salt—a grain of salt will hardly suffice.

When I prescribe a proprietary drug it is usually because I cannot remember its pharmacopoeial equivalent—for example, "dexedrine" and "fersolate." Some proprietary drugs I consider better than their equivalent—for example, "salyrgan" than mersalyl. In my surgery I usually look up the equivalent, but cannot do so when visiting.

In practice, mixtures do give more satisfaction than tablets. Only to-day I visited a lady who had scalded her face and has now got a pain in her back; she told me aspirin does not agree with her but that I had given her some medicine three years ago which acted like a charm. I could not remember it, but on looking up my notes I see that the "magic" draught was mist. acid. acetylsalicyl. Would the department of therapeutics advise me to disclose my petty deception?

The same thing applies to powders; I find that a dose of alkali totally inadequate to neutralize the acid in the stomach, as Professor Maclean taught me, does in fact relieve symptoms (especially if belladonna and bromide be added) better than an adequate dose of powder. Am I to believe the patient or Maclean?

The reason for 12% of prescriptions being skin preparations is that something like 7% of one's patients come on account of skin complaints. I am often astonished at the amount of ointment people manage to consume on quite small areas.

I frankly admit that tonics are placebos. I always drink the samples sent me through the post and have never yet noticed any effect at all; if I am despondent, I am despondent still; if disagreeable, I am disagreeable still. One day I was shocked to see my small daughter drinking her medicine out of the bottle; it seemed lese-majesty. "Oh, but you always do, Daddy," she said—a fact that I had never noticed, expressing, I suppose, my subconscious opinions.

I agree that most of my cough medicines display "therapeutic confusion." Mist. morph. et ipecac. is my favourite (and my patients'). I can only plead that I didn't invent it, and had nothing to do with compiling the *National Formulary*. The British people spend £778m. per year on tobacco to give themselves coughs and peptic ulcers, but to tell patients that is like whistling to the wind. They don't come for advice; they come for medicine. "May one be pardoned and retain the offence?" That is their demand, and advice which even suggests using the will is always resented. All the same, being directly descended from Don Quixote, I never can refrain from giving it—plus medicine as well, of course, or I shouldn't have a practice at all.

When consultants write about colds in the head and the inadequacy of anticatarrhal vaccines I always wonder what experience they have and how they get it. The common cold has few objective signs except a pocket handkerchief completely soaked by 10 a.m. Most people, and it would seem all consultants, are relatively immune, and it would not be worth while giving monthly injections to people who only have a couple of colds lasting three or four days each winter. But when you get a person who has a continuous series from September to April lasting two or three weeks each, with only a few days clear in between, you are called upon to make some effort at prevention. I was such a person, and in the wet autumn of 1917, when under canvas in France (ideal conditions for health, as we were being fattened up for Passchendaele), I had had about four colds by December. The same sort of thing happened in my student days and when I was first qualified, till I began inoculating myself with a well-known anti-catarrhal vaccine in 1921, which immediately cut my colds down to two per winter—real soakers still, lasting three weeks. I continued with monthly injections from September to April year after year, till in 1949 I thought I might have acquired immunity, not having had a bad cold for about 10 years: that winter I escaped, but in 1950–1 I began my three-week soakers again. So now I am back on the vaccine, so far with complete success.

My policy with patients is to recommend vaccine to those who catch "one cold on the top of another," but not to people who have less than four per winter. In adults one may hope to cut down the number of colds in perhaps 50% of cases so selected—and in a much higher proportion in children, but injections are not popular with them.

When punching cards it might be well to remember that family doctors do see an undue proportion of feeble and timid folk: people who would consider as heartless or cruel any suggestion that courage, patience, or fortitude should be used as secondary armaments for combating disease. And I think that does account for, if it does not justify, the alarming number of hypnotics, sedatives, stomachics, and tonics prescribed.

The department of therapeutics must not forget that by cutting off G.P.s from the fellowship of the hospitals at an early age they do reduce the quality of their diagnosis. Hospitals have two functions: treating the sick and training students and keeping graduates up to date. The last of these is not seriously tackled at all. G.P.s don't need to be lectured at: they need to be an integral part of the hospital in the place where they live, with the day-to-day contacts that would give rise to.—I am, etc.,

Norwich. FREWEN MOOR.

SIR,—I have read the Edinburgh prescription survey with considerable interest, and I feel that Professor D. M. Dunlop's searching paper into the prescription habits of medical men (February 9, p. 292) will appeal not only to teachers in medical schools but will prove of considerable value to all students of therapeutics and pharmacy and to any person interested in the historical development of modern medicine. Similar studies were conducted at frequent intervals by the American colleges of pharmacy, and it is hoped to inaugurate prescription studies on a similar basis in this country.

The practical value of individually conducted surveys would be greatly increased and misunderstandings avoided if all investigators were to establish a certain measure of uniformity in their methods of classification. Professor Dunlop and his associates state that the proportion of proprietaries in their sample was about 21%. Considering that the estimate published by the Ministry of Health for prescriptions dispensed during 1949 states that figure to be 16%, this difference is of statistical significance. Either the sample used by the Edinburgh survey is not representative of medical prescribing habits, or the term proprietary is defined differently in both studies. A comparison of Professor Dunlop's figures with those of the Ministry seems to suggest that the Edinburgh survey classifies the various brands of insulin and penicillin preparations as proprietaries, while these products were excluded from the definition of proprietary preparations in the official estimate.

I was told only a few days ago by a person with a strong political bias that the medical profession was trying to undermine the Health Service by recklessly prescribing proprietaries. In support of this argument official statistics were quoted: the proportion of proprietaries prescribed had increased from 16 to nearly 40% during the last two years. Intentionally or unintentionally my informant failed to stress that the latter figure relates to the total cost and not to the total number of N.H.S. prescriptions. I always feel that if people are discussing highly controversial matters they may just as well know what they are talking about.—I am, etc.,

Pinner. H. W. TOMSKI.

SIR,—Professor D. M. Dunlop and his associates (February 9, p. 292) complain that iron is prescribed less frequently than vitamins. Surely there is good authority for prescribing vitamin C whenever iron is given, so that one would expect the total prescribing of the vitamins generally to be greater than iron, and not less as they suggest.

Also many people who have tried a simple iron preparasuch as Blaud's pill and an iron pill combined with folic acid notice that the latter group seem to respond more rapidly. As for "enormous quantities of wool and lint," surely hospitals sending patients with, say, a colostomy home before they have been fitted with a colostomy belt bear some responsibility. And the G.P. might reply to the, what seems to me, irrelevant plaint, that candidates for "*a higher examination*" did not know how to combine cascara and belladonna in a pill, by pointing out that the public seems to buy more of the pills which contain phenolphthalein, which does not need an antispasmodic of the belladonna group to be added, and cascara is "old fashioned."

Finally, the vasodilators, which are rarely used in September, are more popular in winter.—I am, etc.,

Manchester. S. SHUBSACHS.

Coal and Cortisone

SIR,—Dr. Ffrangcon Roberts starts his article (February 9, p. 321) with a preamble concerned to justify cuts in the Health Service. His arguments in this preamble are completely invalid, and I hope the medical profession will decisively reject the ridiculous conclusion that we cannot afford good health.

The figures quoted by Dr. Roberts show that with an ageing population the number of dependants per worker is increasing at a rate of a little over ¼% per annum. On these grounds alone we are told it will be necessary to put proportionately more and more workers into industry to produce the necessities of life, and consequently proportionately less and less workers into medicine (and presumably all other social and cultural activity not directly concerned with industrial production).

If Dr. Roberts had cared to quote the Government Index he could equally well have shown that in recent years the productivity of each worker increased by about 7% per annum. There is no reason to doubt that technical improvement could continue such increases indefinitely. Hence if those who control our economic destiny were so minded they could gear our resources to ever-improving social services without worrying over-much about the ageing population.

Dr. Roberts has, I hope unwittingly, attempted to present as economically inevitable what is in fact a deliberate choice: "Guns before Butter."—I am, etc.,

Brighton. R. S. SAXTON.

A Forgotten Tourniquet

SIR,—With reference to the letters of Drs. C. F. Hadfield and John Ives (February 9, p. 328), please allow a mere physician to pose a question: Has it ceased to be the invariable rule for the tourniquet to be removed before the wound is closed, in order that complete haemostasis may be secured ?—I am, etc.,

Downton, Wilts. J. C. MATTHEWS.

Paying for the Health Service

SIR,—I am indebted to Mr. H. A. Marquand (February 2, p. 272) for drawing attention to an error in my article (January 19, p. 129) and for emphasizing the fact that only one-twelfth of the money spent on the National Health Service came as a grant from the Insurance Fund. May I be permitted to point out that I did mention taxation as a means of financing the Service ? Indeed, in common with my colleagues, I am unlikely to underestimate the importance of taxation in this respect. My object in writing, however, is to repudiate any suggestion that, indirectly or otherwise, I countenance extravagant use of the Health Service.

My only reason for mentioning the finance of the Service was to emphasize that, as the cost of it is now borne at a national level, there is no longer any reason for regional inequalities in the provision of hospital facilities, and that the policy of "fair shares for all" should operate within the Health Service as much as in any other field of social welfare. I think that the bed/population ratios cited in Table II of my article make it apparent that, at any rate in the Birmingham Region, there are considerable differences in available hospital facilities in the various localities. There is, I believe, reason to suppose that such differences exist also in other regions. My contention is, therefore, that it behoves the Ministry of Health to concentrate first on the provision of adequate hospital facilities in those areas in which at present these are deficient.—I am, etc.,

London, S.E.5. VERA NORRIS.

Sexual Disorders in Women

SIR,—I am sure that Dr. P. R. Boucher is correct in his observation (February 2, p. 273) that some women have their erotic sensation limited to the cervix. They seem, however, to be in only a small minority, and I would question his explanation for any inabilities they experience in attaining orgasm. Personally, I think that incomplete penetration is far more likely to be a cause, for this is a factor very commonly present in unsatisfactory coitus and is particularly distressing to women of this sort.

The extended posture, so commonly adopted for coitus, causes the cervix to be quite inaccessible in some women. It also exaggerates any tendency to introital spasm, thus increasing cervical inaccessibility still more. In all quadrupeds the female accepts coitus with her knees to her flanks, and in this position the vagina not only relaxes, but it shortens so that the cervix is properly contacted for insemination.

I agree with Dr. Boucher that a woman with erotic sensation restricted to the cervix may have her orgasm ability lessened by the presence of an occlusive cap: but fortunately the condition is uncommon and presents no serious problem in contraceptive work. More often it is the urethral area—i.e., the anterior and lower third—of the vagina which is the site of a purely limited eroticism. Although these conditions are rare, they should be borne in mind when advising women about sexual difficulties.—I am, etc.,

London, N.W.1. JOAN MALLESON.

Antistin in Habitual Abortion

SIR,—In view of the successful prophylaxis of habitual abortion by means of progesterone implants reported by Dr. P. M. F. Bishop and Dr. N. A. Richards (February 2, p. 244), it is interesting that L. Hirszfeld (*Méd. et Hyg.*, 1950, 8, 299; *Schweiz. Z. allg. Path.*, 1951, 2, 133) has had encouraging results from the use of antistin, both in abortion (habitual and other) and hyperemesis gravidarum. Hirszfeld's allergic interpretation of these conditions is based on his finding, in abortion, of a significant excess of the matings of Rh-negative husband x Rh-positive wife and Rh-positive husband x Rh-negative wife, without any anti-Hr or anti-Rh agglutinins in the maternal circulation.—I am, etc.,

Aberdeen. T. M. ALLAN.

Intra-partum Uterine Rupture

SIR,—I read with interest the medical memorandum by Mr. Robert Hodkinson (February 9, p. 308), but I was very disturbed by his opening paragraph stating that rupture in the lower segment was more dangerous than in the upper segment. It is true that at first I had misinterpreted what Mr. Hodkinson meant, for I thought he was comparing upper with lower segment rupture of a previous caesarean scar. Moreover, his summary of Dugger's work confirmed the misapprehension (actually only the 34 cases in that series were following a previous caesarean section, and the paper does not say that they were classical operations—although they probably were—the remaining 71 were all traumatic or spontaneous). Actually I have since learnt by personal communication with Mr. Hodkinson that he does not think there is much to choose between a lower segment rupture following a caesarean section or that occurring as a spontaneous or traumatic event. It is over this that I wish to take up the cudgels. I agree with him entirely over the danger of the spontaneous or traumatic tear going out into the parametrium and involving the uterine vessels. I have seen two such cases, and very ill they were. But the rupture of the lower segment scar, a rare event, is usually a far less dangerous matter. For evidence to support this statement, I would refer Mr. Hodkinson to a paper read by Dr. Dewhurst and Dr. Rowley before the North of England Obstetrical and Gynaecological Society in January, 1951 (*J. Obstet. Gynaec. Brit. Emp.*, 1951, **58**, 630). Two cases of "silent" rupture of the lower segment scar are described. I have seen a third: a live mother and a live baby were obtained in each case. These cases present like an over-distended bladder due to the unruptured membranes bulging through the uterine defect, and at operation little bleeding is found from the fibrotic margins of the tear. From their own cases and from a study of 66 cases in the literature, Drs. Dewhurst and Rowley conclude that "more time is probably available for diagnosis and treatment whilst the general condition of the mother is still good and the child is alive" than is the case with rupture of a classical caesarean section scar. It is true that some cases were mentioned where damage to the bladder occurred following rupture after the lower segment operation, but I feel that the evidence is sufficient to justify regarding rupture of the lower segment following a previous caesarean section as likely to be a far less dangerous matter than a spontaneous or traumatic tear, and, of course, less dangerous than rupture of a previous classical caesarean section scar. No doubt there will be exceptions, and it would be instructive to hear of them.—I am, etc.,

Bristol. T. F. REDMAN.

Ferrous Sulphate Poisoning in Children

SIR,—Having in the last few days had the supervision of a case of ferrous sulphate poisoning, I am disposed to comment upon Dr. I. O. B. Spencer's excellent paper (November 10, 1951, p. 1112). In it the emphasis was laid on the damage to the central nervous system which is said to occur, in contradiction to the older view that liver damage is the most important feature of these cases. After seeing one fatal case in which the extent of damage to the liver was almost comparable with acute yellow atrophy, I am convinced of the need to protect the liver so far as possible. Since the severe gastritis makes oral feeding not only inadvisable but impracticable for the first 24 hours or more, there would seem to be theoretical advantages in giving intravenous glucose and amino-acids from the start. Vitamin-B complex for intravenous use can be added to the infusion. In the case which is summarized below it was noted that the liver enlarged considerably after 24 hours and became very tender, returning to its normal size after two days.

A boy aged 4 years was admitted at 3.30 p.m. on January 4 with haematemesis and diarrhoea. He was known to have swallowed at least 20 ferrous sulphate tablets some four hours previously. On admission he was mildly shocked, with pallor, coldness of extremities, and a rapid pulse. His state varied from drowsiness to extreme irritability. There were frequent small vomits streaked with blood during the first hour after admission, and he passed three large watery stools. Clinically, there was no dehydration, and there were no abnormal signs in the central nervous system. An intravenous infusion was commenced using casein hydrolysate in 5% dextrose to which an ampoule of B complex for intravenous use (Roche) had been added. He was given two pints (1.2 l.) of this solution in 24 hours. The following day his general condition was improved, but it was found that his liver was enlarged to two fingerbreadths below the costal margin and was very tender. Diarrhoea with tarry motions continued. By the third day he was greatly improved and able to tolerate his diet. The liver had now returned to its normal size. Liver-function tests showed no gross abnormality and he was discharged well on the seventh day.

In a boy of 4 years it is reasonable to suppose that 20 tablets of ferrous sulphate would not prove fatal. However, it seemed to be our duty to try to protect the liver. We should have done better, perhaps, to have fortified the casein hydrolysate with methionine.

One other point: many of the early symptoms of ferrous sulphate poisoning, such as tachycardia, drowsiness, shallow respirations, and mental confusion, are reminiscent of alkalosis, a state which could result from the excessive vomiting. It might be a wise precaution, therefore, to estimate the CO_2-combining power, since we are advised to wash out the stomach with sodium bicarbonate, leaving 10 oz. (285 ml.) of the solution in the stomach, and then follow with bismuth carbonate, 3 gr. four-hourly.—I am, etc.,

Cardiff. R. J. K. BROWN.

Splenins A and B in Rheumatoid Arthritis

SIR,—With reference to Dr. Raymond Greene's paper on rheumatoid arthritis and bleeding time (January 5, p. 17), we have carried out a number of tests of this type at the Royal National Hospital for Rheumatic Diseases. Our mean bleeding time for normal guinea-pigs was 97 seconds (S.D. ± 26 seconds, n = 95). When "splenin A" and "splenin B" extracts from 11 cases of rheumatoid arthritis were injected into guinea-pigs, 80 bleeding-time values for A gave a mean of 124 seconds ± 17, and for B 201 ± 58. Similarly prepared extracts from normal sera gave an A-time of 114 and a B-time of 80 seconds. These figures do not invalidate the claim that an acetone-soluble substance (splenin B) increasing the bleeding time of guinea-pigs can be obtained from the blood of rheumatoid-arthritis cases.

One case of rheumatoid arthritis was investigated in this way before and after splenectomy. Guinea-pigs injected with extracts of the patient's serum before splenectomy gave an average A-time of 119 (S.D. ± 30, n = 24) and B-time of 125 (S.D. ± 39, n = 24). After splenectomy 19 such experiments with the patient's serum resulted in a mean A-time of 99 ± 20 and B-time of 77 ± 23—presumably indicating an absence of B factor, as might be expected from Ungar's theories.

We feel that the guinea-pig bleeding method is so fraught with fallacies that these results should not be taken too seriously, although they support to some extent Ungar's figures. Other methods of investigating this problem are under consideration.—We are, etc.,

G. D. KERSLEY.
D. WATSON.
Bath. L. MANDEL.

Thumping the Chest

SIR,—Two patients encountered recently interrupted their swallow of a thick barium mixture to thump their upper chests with impressive vigour. Both patients suffered from achalasia of the cardia. The disease was at an early stage and only moderate dilatation of the oesophagus was present. The notable feature was a depression of normal peristaltic activity, and barium aggregates formed along the walls of

the upper oesophagus and persisted at these positions for periods varying from one to three minutes. The manœuvre of thumping the sternum was immediately effective in dislodging these clumps and in causing the barium to fall to the lower oesophagus. In one case pain accompanied the barium swallow, and this was promptly relieved by the thumping. The other patient felt occasional pain on swallowing, and at one time when this was severe he had obtained relief by asking his wife to thump his back. The explanation would appear to be that the food or barium causes direct mechanical irritation of sensitive areas of the oesophagus which are the site of hyperaemia or superficial ulceration.

Barium aggregates along the oesophageal walls are not common in conditions other than achalasia, and this may explain why thumping is so effective and has been met with in this condition alone. Patients thump their chests for a variety of reasons, and these range from a feeling of well-being to the first-aid treatment of food that has gone the wrong way, and such a symptom will be difficult to interpret. In combination with dysphagia, however, a history of thumping of the sternum during swallowing may suggest the diagnosis of achalasia of the cardia. It would be useful to know if the manœuvre has been encountered by others and in conditions other than achalasia.—I am, etc.,

Cardiff. BRYAN WILLIAMS.

Infective Gangrene of the Mouth

SIR,—At the Royal Society of Tropical Medicine on December 13, 1951, Dr. D. B. Jelliffe spoke of a form of infective gangrene of the mouth which differs from cancrum oris since it infects the bones (January 26, p. 198). The condition described by Dr. Jelliffe resembles malignant granuloma of the nose, described by R. Woods (*British Medical Journal*, 1921, **2**, 65) and again by S. W. G. Hargrove, J. H. Fodden, and A. J. Rhodes (*Lancet*, 1946, **2**, 596), who stated that about a dozen cases had been described. Hargrove *et al.* treated their patient with penicillin, which improved the local lesion, but the patient died. Most authors state that the cause of malignant granuloma is unknown. I think the cause may be linked up with cutaneous gangrene (*Lancet*, 1945, **1**, 739, and 1946, **2**, 769). Bony changes associated with tropical ulcer were described by J. A. Brocklebank (*Brit. J. Radiol.*, 1943, **16**, 221). There is an account, from the Mayo Clinic, of spreading osteomyelitis of the cranial bones (*Proc. Mayo Clin.*, 1944, **19**, 480). The Mayo Clinic work was based on a paper by H. L. Williams and F. R. Heilman (*Arch. Otolaryng., Chicago*, 1937, **25**, 196) that a micro-aerophilic short-chained streptococcus is responsible for the malignant type of osteomyelitis. The Mayo Clinic workers found this organism sensitive to penicillin. Meleney recommended a special active preparation of zinc peroxide; I have found powdered potassium permanganate effective.—I am, etc.,

Epping. FRANK MARSH.

Incontinentia Pigmenti

SIR,—The article by Dr. A. White Franklin on this subject (January 12, p. 75) prompts me to record a further case recently shown, together with her sister, by Dr. C. D. Calnan at the Dermatological Section of the Royal Society of Medicine (December 15, 1951).

A woman, aged 36 years, and pregnant for the sixth time, was delivered normally of a live female infant weighing 7 lb. 6 oz. (3.3 kg.) on July 30. On the second day of life "several small spots" were noticed and the following day the infant was thought to be suffering from pemphigus neonatorum and was isolated and treated with oral penicillin.

On August 3 the rash was described as a generalized herpetiform eruption, avoiding the palms and soles and confluent on the trunk. There were patches of erythema on the scalp and parts of the back, and the individual lesion was a small vesicle containing golden-yellow material. Culture of the latter was sterile on 48 hours' incubation. By August 5 the rash was clearing off the face and trunk but was confluent and shotty on the lower limbs, while on August 7 the lesions were noticed to be coalescing on the lower limbs and trunk to form subcutaneous plaques. No marked pigmentation was noticed, and throughout the temperature remained normal and the baby's general condition was excellent. Owing to family problems, the mother took her own and her baby's discharge on August 8 and was advised to attend the Hospital for Sick Children, where the diagnosis of incontinentia pigmenti was made.

In 1947 she had been delivered of a female infant, weighing 8 lb. 8 oz. (3.9 kg.), and this baby, too, had developed a skin rash in the neonatal period. Inquiry revealed that this child had incontinentia pigmenti. It is interesting to note that the mother of these two children had been blind in her left eye since childhood, but this was caused by a post-traumatic cataract.

Both these infants were female; neither was premature.

My thanks are due to Mr. R. M. Millen for permission to publish this case and for his helpful criticism, and to Dr. Calnan for his kind help and advice.

—I am, etc.,

Clapton, E.5. F. TAYLOR.

Unsuitable Advice

SIR,—I should be glad if you could find space to publish the following communication addressed to the Secretary of State, War Office, in the interests of the medical and dental practitioners who are serving with the Forces of the Crown. It is strongly urged that medical and dental officers should not terminate their membership of their defence bodies when by doing so they would deprive themselves of an independent medico-legal service which is essential for their individual protection.

"Sir,

"Our attention has been drawn to a Memorandum issuing from the War Office dated January 4, 1952, reference 24/GEN/3172 (AMD.1), denying the need for medical officers of the R.A.M.C. and dental officers of the R.A.D.C. to be members of a defence body.

"We are surprised by the definitive statement of the Director-General in that document that 'it is not considered necessary for R.A.M.C. medical officers or R.A.D.C. dental officers to join a medical or dental protection society in connexion with any treatment, etc., given in the course of their military duties.' This *ipse dixit* is linked to an assurance by a significant proviso—viz., 'If a medical or dental officer is sued as a result of his professional services whilst acting in the performance of his military duties the War Department will stand behind him *provided* that he signs a form of retainer appointing the Treasury Solicitor to act for him. The cost of any resultant settlement of the claim would then be met from Army funds and no financial liability in connexion with the settlement of the claim would fall upon the medical or dental officer concerned.'

"It is, however, more than surprising that the above advice was tendered to officers of the medical and dental services without giving the defence bodies, of which there are three in the United Kingdom, an opportunity of learning in advance the views of the Director-General and of contributing any constructive criticism they might desire to submit on the subject-matter of the Memorandum. To disregard these long-established professional organizations with a total membership of doctors and dentists amounting to 69,500 is to act discourteously.

"Without fear of contradiction, it can be said that the Treasury Solicitor and the Army funds at his disposal will not resolve satisfactorily a diversity of medico-legal situations by which an officer may be confronted and on which the document is peculiarly silent.

"We respectfully submit the following for consideration:

"1. There are occasions we could postulate from our long experience of medico-legal matters when the views that we might entertain for the protection of a medical or dental officer, or for the maintenance of an important principle affecting the profession as a whole, would be diametrically opposed to those held by the solicitor acting for the employing authority of the officer concerned. The interests of a doctor or a dentist do not always run parallel with those of his employer—often they are in conflict. The Treasury Solicitor, for example, may advise settlement of a case out of court when we feel that it should be fought through the courts to support the interests of the officer concerned. The Treasury Solicitor may think that an officer has been negligent in the conduct of his professional work when we think otherwise.

"Medical defence bodies are primarily concerned with defending practitioners whenever it is practicable to do so and of settling cases when the defence is unlikely to succeed. The Treasury Solicitor may have other interests to consider than those of the officer concerned.

"2. A medical or dental officer may require assistance with respect to court-martial proceedings. He may appear at these proceedings in several capacities; as one accused, as prisoner's friend, or as a medical witness; he may stand gravely in need of legal advice or legal representation for his own protection, and this may be of a costly order. (In a recent case £15,000 was spent in the defence of a medical officer.) Surely in the foregoing circumstances the Treasury Solicitor would be unwilling or indeed unable to furnish advice or provide representation.

"3. A medical or dental officer may find himself in acute disagreement with his employing authority with regard to his care and treatment of a military or civil patient, or with regard to the terms and conditions of his service, affecting rank, remuneration, or pension. He may be accused of libel or slander, or of some other civil or criminal offence arising out of or associated with the pursuit of his professional work. He may be called upon to appear at a military inquiry, a civil court, or the General Medical Council, and would need expert assistance to examine, prepare, and proffer a defence or a plea in mitigation and to avoid, if possible, detriment to his future in the Service.

"These situations demonstrate the necessity for the officer concerned to be able to resort to an independent defence body for appropriate personal help when necessary, and to assert, as is done in the Memorandum, that he could disregard the need for membership of a medical defence organization in the circumstances described therein is but to induce a sense of false security in the mind of an officer reading that document and to give advice that is incomplete and misleading.

"Though it is regrettable to disagree in public with the Director-General on a matter affecting medical and dental officers, it is clearly my bounden duty, as secretary of the body I serve, to warn these practitioners of the inadequate nature of the protection proffered in the Memorandum quoted above and of the continued need for them to maintain throughout their professional careers their membership of a defence organization to secure the availability of independent advice, legal representation, and financial indemnification when required.

"In view of the action already taken and about to be taken I have no alternative but to arrange for the early publication of this letter in the professional press."

—I am, etc.,

The Medical Defence Union, London, W.C.1. ROBERT FORBES, Secretary.

Action of Different Insulins

SIR,—The search for a type of insulin which will give a more constant control of blood sugar levels in diabetes continues, and Dr. F. Gerritzen's interesting article (February 2, p. 249) gives examples of the duration of action in 10 different types of insulin used on normal persons. Those who are interested in the treatment of diabetes are glad to have any information on new varieties of insulin even if some of them are, for commercial reasons, not in general use in this country.

With regard to the insulins which are available here, I suggest it might be unwise to assume that a similar action to that described in the article mentioned necessarily applies in diabetes owing to a greater fluctuation in the levels of blood sugar and to the greater variation in sensitivity in diabetics as compared with normal persons.

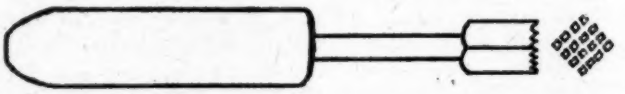
As many diabetics are more afraid of hypoglycaemic attacks than of diabetes itself, the assumption that the action of protamine zinc insulin begins to wane after eight hours and is complete by 16 hours might lead to more nocturnal attacks, due to falling blood sugar, than are already encountered. It would also be useful to know whether the mixed insulins were given in the standard English way or in the American fashion—that is, a complete mixing giving rise to a fixed amount of soluble remaining in the mixture.—I am, etc.,

Warrington. R. GUEST GORNALL.

Polycentron

SIR,—Recently I published a paper (Chrysanthis, 1948) on the comparative value of the two classical methods of vaccination, the multiple-pressure method and the standard scratch one, expressing myself in favour of a combined method of vaccination. But many authors, as Dunley and May (1932), Parish (1944), Mole (1947), and Lovett (1947), find the multiple-pressure method more ideal. However, when applying the multiple-pressure technique I observed that it is rather more tiresome than the scratch one, especially when vaccinating a great number of people. In order to lessen this disadvantage of multiple-pressure technique of vaccination I invented an instrument, the "polycentron."

This (see Fig.) consists of two parts: a wooden handle of 5 cm. length, and a hard steel stalk of 3.5 cm. length, which fits into a block 1 cm. long and diameter 0.7 × 0.7 cm. The



lower surface of the block has 16 spikes, each of them protruding 0.15 cm. The vaccinator, after cleaning the skin, places a drop of calf lymph on the skin and presses the polycentron on it once or twice. So the vaccinator makes only one or two pressures, instead of 30–40 pressures with a needle as is required by the standard multiple-pressure technique of vaccination. The shortening in required time is obvious. This is more important when vaccinating a great number of people, as in schools and in the Army.—I am, etc.,

London, W.2. KYPROS CHRYSANTHIS.

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Habitual Abortion

SIR,—I read with great interest the article by Drs. P. M. F. Bishop and N. A. Richards on habitual abortion (February 2, p. 244) and appreciate their remarks about my own series of cases. From my own results two interpretations are possible: that the usually accepted spontaneous cure rate after three or more abortions is wrong; or that the treatment these patients received was sufficient to alter the foetal survival rate. I am reluctant to accept the first hypothesis, but am sure that the medicinal treatment patients received was insufficient materially to affect their chances.

I am not a great believer in the effect of psychology on organic disease, but am prepared to accept the fact that the emotions such as fear and anxiety can alter menstruation, presumably by action on the pituitary. The logical thing to do is to give these patients no treatment whatever, and this is being done by one of my colleagues.

I await with great interest the results of a series of patients treated by Drs. Bishop and Richards with the implantation of inert tablets.—I am, etc.,

Manchester. D. C. A. BEVIS.

Thank You

SIR,—I am writing this short letter to thank those members of the medical profession who subscribe so generously to the funds of the Royal Medical Benevolent Society, thus enabling that organization to distribute regular pensions and welcome Christmas cheques to doctors who have to contend with ill-health and subsequent poverty. This short note is brief indeed, but it expresses the maximum of gratitude.—I am, etc.,

RECIPIENT.

POINTS FROM LETTERS

Succinylcholine Chloride

Dr. R. BLAIR GOULD (London, W.1) writes: In the literature accompanying this product occurs the following statement: "In the dose recommended . . . it produces a paralysis which lasts for about three minutes. Spontaneous respiration then returns. . ." Since apnoea lasting 20–40 minutes is not uncommon after this drug, it would appear that the statement should be accepted with considerable caution.

Obituary

H. D. DAKIN, D.Sc., F.R.S.

Dr. Henry Drysdale Dakin, whose name is perpetuated by the hypochlorite solution he brought into use during the first world war, died at Scarborough-on-Hudson, New York, on February 10. He was born in London on March 12, 1880, the son of a Leeds iron and steel merchant. From the Leeds Modern School he went on, after a period of apprenticeship with the Leeds city analyst, to the Yorkshire College (now Leeds University), where he won an 1851 Exhibition Scholarship. It was about this time that he decided to take up the study of biochemistry, and from Leeds University, where he took the degree of D.Sc. in 1909, he moved on first to the Lister Institute and then to Heidelberg. In 1905 he went to the Herter Laboratory in New York, and thus began his long and distinguished career as a medical research worker in the U.S.A. Many honours came his way. He was elected a Fellow of the Royal Society in 1917, and the universities of Heidelberg, Leeds, and Yale conferred on him honorary degrees. In 1941 he received the Davy Medal of the Royal Society for his pioneer work in biochemical research, and for his contribution to the study of intermediary metabolism.

We are indebted to Sir Charles Harington for the following appreciation of Dakin's contribution to medical science: By the death at the age of 71 of Dr. H. D. Dakin, following closely on that of the late Professor H. S. Raper, biochemistry has lost another of the remarkable group of men trained under the late J. B. Cohen, of Leeds, who have done so much for the development of the subject in many different directions.

Dakin's early interest in biochemistry was aroused by a period of work with Kossel, during which the enzyme arginase was discovered. At the Lister Institute, where he worked for a few years, he made another important contribution in being the first to demonstrate the stereochemical specificity of enzymes in his study of the action of esterases on the esters of the active mandelic acids. During his time at the Lister Institute Dakin also published a synthesis of adrenaline.

In the early years of the present century Dakin went to New York to work in the laboratory of the late Christian A. Herter (whose widow he subsequently married). Here he soon became deeply involved in the researches for which he will always be best known—namely, the study of the intermediary metabolism of amino-acids and fatty acids. In this field, at that time practically unexplored, he made great contributions, on which much modern knowledge rests. His attack on the problem of fatty acid oxidation was made in parallel with that of Knoop in Germany; the result of the two investigations was to establish the nature of the process (β-oxidation) by which fatty acids are utilized in the animal body, and Dakin made the important observation that this process, as well as other biological oxidations, could be imitated *in vitro* by the use of hydrogen peroxide. Later, also in Herter's laboratory, Dakin returned to work on enzymes, and, in collaboration with the late H. W. Dudley, discovered and studied the properties of the enzyme glyoxalase.

During the 1914–1918 war Dakin worked on this side of the Atlantic, both in this country and in France. His main contribution was the development of the buffered hypochlorite solution which became known by his name, and which found important application in the irrigation of infected wounds.

Apart from his work on enzymes and biological oxidations, Dakin's main scientific interest was in the chemistry of proteins and amino-acids, and it was to this subject that he devoted himself when he established his private laboratory at Scarborough-on-Hudson on his return to the United States after the war. His discovery of the racemizing effect of alkali on proteins enabled him to expose features of protein structure which at that time could not be revealed by other means. He also introduced new methods of separating amino-acids which made possible the more accurate determination of the composition of proteins. Although Dakin's methods have been rendered obsolete by the great advances in this field in recent years, his were pioneering studies in a subject that has proved to be of the greatest importance for biology.

Having much of the artist in his temperament, Dakin was essentially a lone worker. During the whole of his career he had few collaborators and he trained no pupils. Indeed, his only sustained collaboration was with H. W. Dudley, and this was based on close personal friendship as well as on community of scientific interest. Nevertheless any assessment of Dakin's contribution must take account not only of his personal scientific achievements, great as these were, but also of the very considerable influence that he exercised, in ways that did not appear on the surface, through his friendships with scientific colleagues. This influence and his own work combine to give him an outstanding place among those responsible for the development of modern biochemistry.

E. BRIGHT VEDDER, M.D., D.Sc.

Colonel Edward Bright Vedder, a distinguished United States Army medical officer, died in the Walter Reed Memorial Hospital, Washington, on January 30, at the age of 73.

He was born in New York and received his medical education at the University of Pennsylvania medical school, where he graduated M.D. in 1902. For a short time after this he collaborated with Simon Flexner, who was then studying the aetiology of bacillary dysentery. Vedder was commissioned in the Army in 1903, and participated in early typhoid immunization experiments. During later service in the Philippines he studied beriberi and found it to be associated with the eating of polished rice. It was as a result of this observation that he introduced the successful measure of substituting half-polished rice to supply the dietary deficiency, later found to be vitamin B_1. His monograph on beriberi (1913) won for him the Cartwright Prize of the College of Physicians and Surgeons of Columbia University. His work on clinical scurvy also led the way to further discoveries. In 1932 he was awarded the Wellcome Prize for his *Study of the Antiscorbutic Vitamin*. He also made important contributions to the knowledge on sprue, leprosy, and syphilis. In 1911 his demonstration of the amoebicidal action of emetine led to its general adoption in the treatment of amoebic dysentery. From 1922 to 1925 Vedder was chief of the medical research division at Edgewood Arsenal, and senior member of the U.S. Army Board of Research from 1925 to 1928. In 1930 he was appointed director of the Army Medical

School at Edgewood. He retired from the Army in 1933 and spent the next ten years as professor of pathology and experimental medicine at George Washington University.

Dr. WILLIAM DONALD MACKINNON, district medical officer at Portree, Isle of Skye, died suddenly on January 12, aged 59. He was a son of the late Reverend D. Mackinnon, who was at one time minister at Wanlochead, Dumfries. From Herriots School he went on to Edinburgh University, where he had a distinguished career as a student. He gained a first-class certificate for almost every class and no less than eight medals. After graduating M.B., Ch.B. with distinction in 1917, he joined the R.A.M.C. and saw service in France. After demobilization he held a number of hospital posts, including that of senior assistant and deputy superintendent of the Southern General Hospital, Glasgow. He there met his future wife, Dr. Mary MacDonald, who was his colleague on the staff. In 1922 he was appointed medical officer to the parish of Strath, in Skye. Strath was the traditional home of the Mackinnons, and that for him was one of the attractions of the post. In what now appear to be far-off days he almost always wore a kilt of his clan tartan. While in Strath he was superintendent of the Mackinnon Memorial Cottage Hospital, and he did some emergency surgery there. Two years later he went to the neighbouring parish of Portree, where he also had charge of the Skye District Infectious Diseases Hospital. In the British Medical Association he held office as secretary of the Islands Division from 1926 to 1939, and he was president of the Northern Counties of Scotland Branch from 1937 to 1938. He also served for many years on the Inverness county panel committee. A keen freemason, he was a member of several Chapters, including the Inverness Sovereign Chapter and Past Master of two lodges.

A. L. writes: Although his health had not been good for a number of years, the sudden death of Dr. W. D. Mackinnon came as a sad shock to his many friends. It was almost as if it required his death to make them realize how deep was their affection for him. Those who knew him only during the last few years can have had little idea of the liveliness of his intelligence or the catholicity of his mind in days gone by. It is possible that if he had followed hospital rather than general practice he would have more fully fulfilled his youthful academic promise. He could with ease have passed any examination he set his mind to, but he was entirely devoid of vulgar ambition. During the last few years he was dogged by illness, but, like other difficulties, he took it in his stride and made light of it. It was never an excuse not to see a patient nor to attend a meeting. He was devastatingly frank and honest and assumed the same qualities in all with whom he had dealings. There might not always be universal agreement with him, but no one doubted his sincerity. His home, for which much credit must go to his wife, was a centre of hospitality for many people, both medical and lay. Much sympathy goes out to Dr. Mary Mackinnon, who did what she could, so far as he would permit, to lighten his work recently, and to their son and daughter.

Dr. PRESTON RICHARD WALLIS died on January 26 in Jersey, Channel Islands, where he had lived and worked for more than 30 years. The grandson, son, and brother of medical men, he qualified at University College Hospital in 1896. He practised in London for a time, and became honorary anaesthetist at the East Ham Hospital. In Jersey also he built up a reputation as an efficient and careful anaesthetist. A colleague has sent us the following account of two incidents in which Dr. Wallis figured during the German occupation of the Channel Islands. One bitterly cold night Dr. Wallis was called to see a sick child of a humble family. He found there the remnants of the last inner door smouldering in the fire, while some members of the family were busy smashing up the only remaining table in the house in order to provide fuel. After attending to the child, Dr. Wallis said he would return presently. He went to his home and by candlelight scraped together the last bits of coal left in the coal cellar and filled a sack, carried it back to the cottage of his patient, and left it at the door. His only words, almost in apology, were, "You see, in my house the heat of those coals would now have chilled me, so you are welcome to them." Another example of his heroism, until now unrecorded, occurred when he was called to see a woman patient who was married to a helpless invalid. The woman, a Jewess, was under orders to report in two hours for transportation to the Belsen extermination camp. She pleaded that he should humanely destroy her. Instead the doctor bundled her into a sack and placed her in the back of his car, under the very nose of the Gestapo, who had her under constant observation. Dr. Wallis knew full well that if caught in this act he would have been shot without a trial, or, at best, would have been transported with the woman. He managed to drive her to the home of some good patients, where she was concealed in the attic and kept and cared for until the liberation. Many people in Jersey and elsewhere will know from their own personal experiences how much they owe to Dr. Wallis, both as physician and as friend.

Dr. CHARLES SEFTON O'NEILL, whose death occurred after a short illness on February 2, spent most of his life in the vicinity of Manchester. He graduated M.B., Ch.B. at the Victoria University in 1903, having won the prize in clinical medicine at the Royal Infirmary. He took the D.P.H. in 1904, and proceeded M.D. with commendation in 1907. After no fewer than three hospital residencies—which fitted him for a busy and successful life in general practice—he went into practice at Hale, Cheshire. There was a break of three years in the first world war when he was able to develop his special interest in radiology in a mobile unit in France, where later he became director of radiology for the Third Army. He was mentioned in dispatches, and later appointed O.B.E. In 1919 he went back into practice—or what was left of it—and he busied himself in what became one of his happiest pursuits, the founding and running of a local medical club. Apart from the B.M.A.—of which O'Neill was a most active member, being chairman of the Mid-Cheshire Division from 1922 to 1924—there was nothing to promote friendship and professional gatherings in the locality, and he felt keenly the need for it. The club which he founded thrived under his unstinting care, and has been a blessing and rallying point for its many members ever since. A few days before his death he announced with quiet satisfaction that he had missed only one meeting of the club in over 30 years. He was originator, treasurer, secretary, and—in the best sense—dictator of it: in these multiple capacities he was constantly in touch with a large local medical circle and also with most of the specialists of the Manchester area. In addition he was an ideal host both to the profession and a large group of friends. Possessors of an "all-the-year-round" flower garden, and keen connoisseurs of a well-stocked vegetable garden, Charles O'Neill and his wife kept the happiest of homes, ever open to welcome friends, consultants, and fellow practitioners alike. A gracious and hospitable atmosphere, alert with interest in the arts and literature, but never overburdened with it, produced its inevitable meed of pleasure and satisfaction in both hosts and guests. In addition to running a big practice, Dr. O'Neill continued from 1919 until two years ago as honorary radiologist to the Altrincham General Hospital, a task which became increasingly onerous and heavy. He many times made himself "royal beggar" for the department, much valuable plant being installed as a result of his unfailing ability in unearthing contributory sources in North Cheshire. Remembering the lean days of 1919, he worked constantly for the protection of practices in the second world war: many returning practitioners to his district had cause to

be grateful to him for his work. He was not wholly opposed to the National Health Service—but firmly opposed to a 100% Service and to the unlimited powers vested in the Ministry of Health. The cares, responsibilities, and privileges of practising medicine were to him very vital, and he had the vision to see and dread the possible degeneration of a tradition when these responsibilities are removed from the control of those who have been trained to accept them. An individualist rock-set in a gathering sea of conformity, O'Neill's passing will be noted by a vast circle of friends and medical brethren with profound regret.—P. H. M.

Medico-Legal

TUBERCULOSIS CONTRACTED BY NURSE

APPEAL SUCCEEDS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

An Industrial Injuries Tribunal has allowed the appeal[1] of a Dundee nurse against a decision of an insurance officer that she was not entitled to industrial injury benefit in respect of tuberculosis which she said was contracted by nursing tuberculous patients.

The nurse, who is now 20 years old, started work as a student nurse in 1947. Before she started she had a medical examination including chest radiography. The result was negative. She worked in several wards as a resident nurse, including a whooping-cough ward. She said that some of the cases she nursed at that time had tuberculous complications, as she knew from entries on the patient's charts, and one at least was later transferred to a tuberculosis ward.

In January, 1948, as a result of a routine *x*-ray examination which turned out positive she was admitted to a chest hospital. By January, 1949, after a further *x*-ray examination she was told she was fit to resume work on light duties at first.

She returned to work in a hospital in that month, doing ambulance work and no ward work for the first few months. During that time she dealt with all types of cases that came to the hospital, including cases of "open" tuberculosis. In November, 1949, she was again found to be suffering from tuberculosis, and was again admitted to hospital, where she remained until discharged in April, 1951.

The insurance officer had rejected her claim on the ground that there was no record by the hospital that any of the patients whom she had nursed before January, 1948, were suffering from tuberculous complications. Pulmonary tuberculosis had been diagnosed in January, 1948, before she had come into close and frequent contact with the "open" cases of tuberculosis in the course of her ambulance work, and therefore he did not find that the disease from which she was suffering was due to the nature of her employment. This view was supported in a specialist's report.

In allowing the appeal the chairman of the tribunal said that the nurse was entitled to rely on the presumption in the regulations that the disease was due to the nature of her employment unless the contrary was proved. The tribunal was not satisfied beyond reasonable doubt that the disease was contracted otherwise than as a result of her employment. No satisfactory evidence to that effect had been forthcoming, and the tribunal found in the terms of the regulations that the contrary had not been proved. The nurse will receive 19s. per week extra benefit accordingly.

[1] *The Scotsman*, September 14, 1951.

Universities and Colleges

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College, held on February 14, with the President, Sir Cecil Wakeley, in the chair, Loyal Addresses of Condolence to Her Majesty the Queen and to Her Majesty Queen Elizabeth the Queen Mother were adopted.

The Hallett Prize was awarded to J. C. N. Wakeley (King's College Hospital) and a Moynihan Lectureship to Dr. L. Mayer (New York). The award of Prophit Research Studentships to F. Masina and T. R. Munro was reported.

Mr. L. E. C. Norbury and Mr. A. Dickson Wright were nominated as members of the Council of the Imperial Cancer Research Fund.

The Council gratefully received gifts of silver from the Faculty of Medicine of the University of Ceylon.

Diplomas of Membership were granted to D. W. Ebrahim and B. G. Jackson and to the recipients of the Licence of the Royal College of Physicians of London whose names were printed in the report of the meeting of the Royal College of Physicians of London in the *Journal* of February 9 (p. 335).

Diplomas were awarded, jointly with the Royal College of Physicians of London, to the following successful candidates:

DIPLOMA IN PUBLIC HEALTH.—J. P. Agrawal, Frances C. Myatt, T. A. Pace, A. C. B. Singleton, W. J. Smither, E. D. H. Williams.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—M. Lwin.

The following hospitals were recognized in respect of surgical posts required of candidates for the Final Fellowship examination: Bury General Hospital (re-designation of posts), registrar; registrar (orthopaedic); senior house-surgeon; senior house-surgeon (orthopaedic); and two house officers, all for six months. Memorial Hospital, Darlington, two surgical registrars, each for one year; surgical house officer (house-surgeon), for six months. Nelson Hospital, Merton, senior house-surgeon, for six months. St. Mary's Hospital, Portsmouth, temporary recognition to be extended for one year. Queen Alexandra Hospital (Army), senior house officer (ophthalmology); senior house officer (otolaryngology) to be recognized for six months for general surgery. Kent and Sussex Hospital, Tunbridge Wells, re-designation of registrar post, already recognized to that of senior house officer (ear, nose, and throat). Tindal Hospital, Aylesbury, additional recognition, house-surgeon, for six months. St. James's Hospital, Leeds, additional recognition, deputy resident surgical officer, one year; first house-surgeon and second house-surgeon, both for six months.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College, held on January 26, with the President, Dame Hilda Lloyd, in the chair, the following were elected to the Fellowship: Y. N. Ajinkya, A. W. Andison, A. Josephine M. T. Barnes, C. W. F. Burnett, W. D. A. Callam, G. P. Charlewood, S. Davidson, R. de Soldenhoff, A. B. Evans, D. B. Fraser, H. F. P. Grafton, G. G. Lennon, W. A. Liston, R. Lyons, H. McLaren, R. F. Matters, B. E. Meek, H. K. Porter, P. G. Preston, D. C. Racker, G. W. Robson, J. W. Schabort, G. G. L. Stening, S. L. Townsend, J. C. Whyte, R. J. Wotherspoon. N. McA. Gregg was also elected to the Fellowship in recognition of his work on rubella in pregnancy.

Lydia Colaco was admitted to the Membership of the College.

The following were elected to the Membership: E. McL. Barbour, Caroline D. Baugh, R. M. C. G. Beard, D. C. G. Bracken, A. D. H. Browne, K. McL. Crocker, V. Drosso, M. P. Durham, J. Elstub, B. Eton, M. R. Fell, H. Ferguson, W. T. Fullerton, R. L. Gadd, F. G. Geldenhuys, A. I. I. Klopper, J. B. Lawson, Sarah Lehane, R. D. Macbeth, A. D. McIntosh, D. Magner, D. J. Meagher, A. P. B. Mitchell, N. Moss, T. R. Nelson, E. P. D. O'Neill, C. B. Oxner, J. Price, Monica M. A. Reford, W. H. D. Scotland, H. I. Schmilg, R. S. L. Stafford, Joan E. Storey, E. Sussman, J. S. Tomkinson, F. L. A. Vernon, J. Ward, P. P. Wium.

The Sims-Black Travelling Professor, Mr. G. F. Gibberd, left for South Africa on January 31, on the first stage of his tour.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending February 2 (No. 5) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	24	2	14	0	0	51	5	20	3	4
Dysentery	490	56	78	3		967	62	189	7	1
Encephalitis, acute	5	0	0	0		3	0	1	0	1
Enteric fever:										
Typhoid	5	0	1	1	1	3	0	1	0	1
Paratyphoid	6	0	0	0		3	0	0	0	
Food-poisoning	94	6		0		139	43		0	
Infective enteritis or diarrhoea under 2 years				7	29				13	9
Measles*	3,386	50	319	160	43	16,321	2368	161	28	100
Meningococcal infection	31	1	17	2	2	73	6	18	4	3
Ophthalmia neonatorum	30	2	9	0	1	36	0	8	0	
Pneumonia†	1,005	55	308	11	1	3,513	167	466	104	132
Poliomyelitis, acute:										
Paralytic	17	3	1	1	2	21	0	3	0	1
Non-paralytic	8	1				11	2			
Puerperal fever§	257	46	8	1	2	87	8	9	2	
Scarlet fever	1,320	109	241	16	31	875	65	149	35	39
Tuberculosis:										
Respiratory			157	35				200	23	
Non-respiratory			25	4				30	5	
Whooping-cough	2,652	83	345	120	53	4,916	428	685	22	90

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0		0	0	*0*	0	*0*	0	0
Dysentery	2	1		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	18		1	0	2	*11*		*0*	1	2
Influenza	47	9		3	0	*1,269*	142	*54*	19	73
Measles		0		0	0		0	*0*	0	0
Meningococcal infection		0					0	*0*		
Pneumonia	341	59		18	9	*830*	116		32	29
Poliomyelitis, acute	4	0			0	*2*	0			0
Scarlet fever		0		0	0		0	*0*	0	0
Tuberculosis:										
Respiratory	170	20	21	4	6	*246*	36	*32*	2	14
Non-respiratory		1	0	1	3		3	*5*	0	1
Whooping-cough	4	0		0	0	*9*	1	*3*	0	2
Deaths 0–1 year	275	25	38	10	17	*270*	33	*35*	8	20
Deaths (excluding stillbirths)	6,938	1008	837	168	216	*10,141*	1568	*926*	185	444
LIVE BIRTHS	7,457	1117	857	208	329	*6,892*	1095	*919*	253	384
STILLBIRTHS	185	22	26			*177*	22	*27*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Smallpox in Lancashire

There is laboratory confirmation of the diagnosis of variola in a cotton worker resident in Milnrow, Lancs. The woman was unvaccinated. The rash appeared on February 1, fever and constitutional disturbance having started on January 29.

The patient was removed to a smallpox hospital on February 8. Her husband sickened on February 14 and developed a rash on February 17; her daughter sickened on February 16; both were removed to hospital on February 17.

Temperatures of 102° F. (38.9° C.) were recorded during the prodromal stage; thereafter the disease was mild. The rash was discrete and sparse, but the distribution typical of variola minor.

It now seems probable that similar cases exist in the adjacent town of Rochdale, and the matter is being investigated.

Mysterious Rash at Cheltenham

A small outbreak of a puzzling dermatological affection at Cheltenham is reported by the M.O.H., Dr. Donald E. Morley. The first wave of cases began early in January. It was not of long duration, and by the third week in January very few cases were occurring. A second wave appeared in the first few days of February, and the outbreak continues. As the condition is not notifiable and has no serious effects its exact incidence is unknown. But it is estimated that at least 200 cases have occurred, and possibly many more.

The eruption is follicular and of a discrete papular type, with localized irritation; normally there are no general symptoms except occasionally some malaise or vomiting. In a very few bad cases in young children there have been a moderate adenopathy and mild pyrexia. The face, including the retro-auricular region, is most commonly affected. Next in frequency are the back, forearms, abdomen, and legs. After a day or two the rash becomes less prominent, but horny plugs appear in the follicles, and the skin feels like a nutmeg-grater. The eruption disappears in 4–10 days.

The incidence is highest in women and young children, and evidence is still inconclusive about the infectivity or not of the condition.

Investigations into the aetiology and epidemiology of the disease are in progress. Outbreaks may be occurring elsewhere in the country, which, owing to the mildness of the infection, are escaping any significant attention. It is hoped that doctors seeing this condition will inform the M.O.H.s. concerned and that the latter will send the relevant facts to the Ministry of Health (S.M.O., Med. 3), Savile Row, W.1.

Infectious Diseases

In England and Wales during the week ending February 2 an increase was recorded in the number of notifications of measles 549, acute pneumonia 169, and whooping-cough 79, and a decrease of 57 for dysentery.

The notifications of scarlet fever were 27 more than in the preceding week, and only small changes occurred in the general distribution of the cases. A small rise in scarlet fever was recorded in London and each of the south-eastern counties, and the number of notifications for the combined area was 69 more than in the preceding week. The largest rises in the notifications of measles were Norfolk 81, Cheshire 79, Lancashire 67, and Middlesex 75. The notifications of diphtheria were 3 fewer than in the previous week. The chief feature of the returns for diphtheria was the reappearance of diphtheria in the city of Birmingham, where five cases were notified during the week. The largest variations in the trends of whooping-cough were a rise of 48 in Warwickshire and a fall of 63 in Yorkshire.

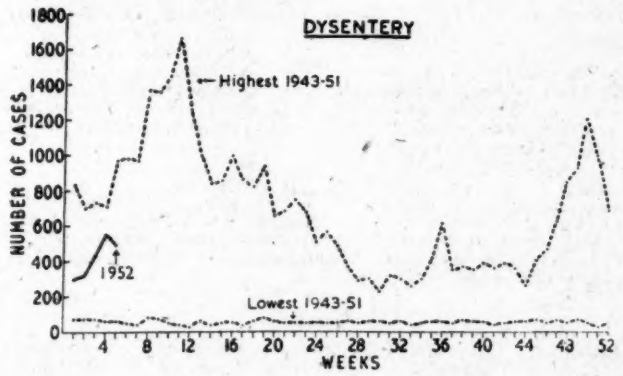
West Riding. The rise in the incidence of acute pneumonia was most pronounced in London and the south-east counties, where 72 more cases were notified than in the previous week.

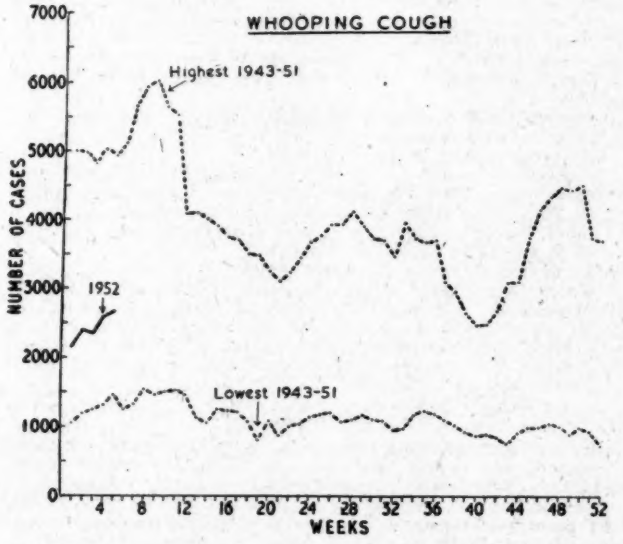
The number of notifications of acute poliomyelitis was one fewer than in the preceding week for both the paralytic and non-paralytic cases. The largest return during the week was 4 in London.

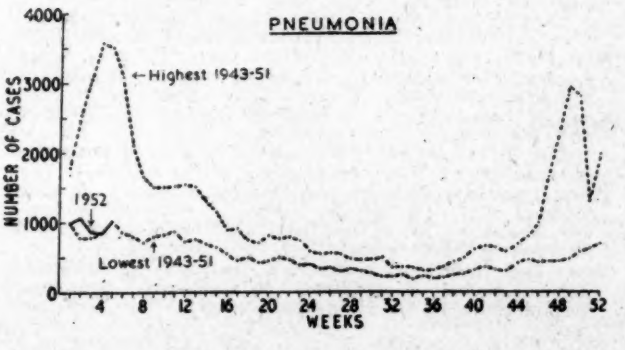
The chief centres of dysentery were Norfolk 73 (Norwich C.B. 61); Middlesex 72 (Willesden M.B. 33, Ealing M.B. 10); London 56 (Islington 16, Camberwell 10); Lancashire 54; Yorkshire West Riding 50 (Bradford C.B. 23, Leeds C.B. 10); Warwickshire 22 (Birmingham C.B. 15); Devonshire 21.

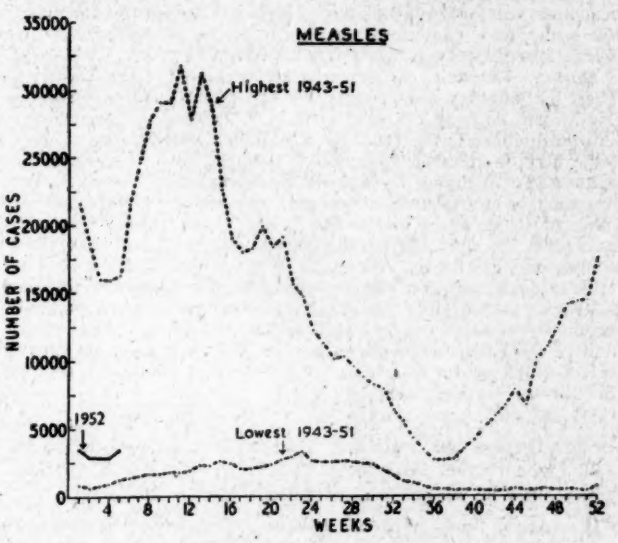
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus ---------, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending February 9

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,416, whooping-cough 2,686, diphtheria 34, measles 4,425, acute pneumonia 1,105, acute poliomyelitis 17, dysentery 592, paratyphoid fever 6, and typhoid fever 2.

Medical News

Birthday of the Week.—The British Association of Physical Medicine, founded in 1943, has decided to publish its own quarterly journal, and the first issue of *Annals of Physical Medicine* is out this week, published by Headley Brothers, Ltd., 109, Kingsway, London, W.C.2, at 6s. a copy or a guinea a year. It contains two papers—one an experimental study of the biological effects of micro-waves (centimetric radio waves), the other an account of the ambulant treatment of the complications of varicose veins in over 500 patients. In addition there are book reviews, news, and a useful abstracting section from the *International Review of Physical Medicine and Rehabilitation*. The new journal is very neat in format, and contains an excellent photograph of Lord Horder by way of frontispiece.

Whole-time Specialists.—The first annual dinner of the Association of Whole-time Salaried Specialists was held at the Royal College of Surgeons of England on January 25 and was attended by approximately 60 members. The guests included Sir Max Page, representing the Royal College of Surgeons, Mr. R. E. Jowett, president of the Regional Hospitals' Consultants and Specialists Association, and Mr. J. M. Milloy, of the Medical Superintendents' Society.

Medical Research Council Fellowships.—The Medical Research Council invites applications for the following Travelling Fellowships for the academic year 1952–3:

Rockefeller Travelling Fellowships in Medicine.—These Fellowships are provided from a fund with which the Council has been entrusted by the Rockefeller Foundation of New York. They are intended for graduates resident in this country who have had some training in research work in clinical medicine or surgery, or in some other branch of medical science, and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad, before taking up positions for higher teaching or research in the United Kingdom. The stipend of Fellowships tenable in the United States will ordinarily be at the rate of $2,600 per annum for a single Fellow, and of $3,600 per annum for a married Fellow. Travelling expenses and some other allowances will be paid in addition.

Eli Lilly Travelling Fellowships in Medicine.—These Fellowships, tenable in the United States, will be provided from a special fund placed at the disposal of the Council by Eli Lilly and Company, U.S.A. Four Fellowships will be available for the

academic year 1952–3, and the awards will in general be made on terms and conditions similar to those attaching to the Rockefeller Travelling Fellowships in Medicine.

Dorothy Temple Cross Research Fellowships in Tuberculosis.—These Fellowships are awarded by the Council from a special endowment of which it is trustee. The object of the Fellowships, as defined in the Trust Deed, is to give special opportunities for study or research to suitably qualified British subjects of either sex "intending to devote themselves to the advancement by teaching or research of curative or preventive treatment of tuberculosis in all or any of its forms." The Fellowships will, as a rule, be awarded to candidates who wish to make their studies or inquiries elsewhere than in the United Kingdom. The Fellowships provide for the payment of stipend, together with an allowance for travelling and incidental expenses. The stipend will ordinarily be at the rate of £650 per annum for a single Fellow, and of £900 per annum for a married Fellow, subject to appropriate adjustment in the case of Fellowships tenable at centres outside the sterling area.

Further particulars and forms of application may be obtained from the secretary, Medical Research Council, 38, Old Queen Street, Westminster, S.W.1, with whom applications must be lodged not later than March 15, 1952.

London's New Medical Officer.—The impending retirement of Sir Allen Daley, Medical Officer of Health and School Medical Officer of the London County Council, was announced in the *Journal* of December 8, 1951 (p. 1393). As we go to press we learn that at a meeting of the L.C.C. on February 19 Sir Allen Daley's deputy, Dr. John Alexander Scott, has been appointed in his stead. Dr. Scott, who was born in 1901, became deputy in 1948.

Biological Warfare.—Over 200 scientists wanting to co-ordinate their efforts for peace met in London in January, 1951, and elected a provisional committee to draw up proposals which could be submitted to a national conference of scientists. Such a conference was held in London last month, attended by about 180 eminent scientists; the resolution passed at the International Congress of Microbiology at Copenhagen in 1947 condemning all forms of bacteriological warfare was warmly approved. The conference called upon the Government "to enter into negotiations with other Governments with a view to a general formal repudiation of any use of biological warfare and to work out practical measures to ensure that this repudiation is effective." It further asked that secrecy should not be imposed on workers engaged in research connected with biological warfare, that inspection of their laboratories should be allowed, and also the publication of results.

Emergency Bed Service: Applications and Admissions.—During the seven days ending February 18 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,195, of whom 87.53% were admitted.

COMING EVENTS

Nursing Conference.—The Royal College of Nursing is holding a conference on the mental health services from February 27 to 29 at the College (Cavendish Square, W.1). The fee for the conference is £2 2s., and details may be obtained from the secretary, Royal College of Nursing.

Sub-fertility Conference.—The Family Planning Association is organizing a conference at the Bonnington Hotel, Southampton Row, W.C.1, on February 29 and March 1. Full details from the secretary, Miss I. M. James, 64, Sloane Street, S.W.1.

Service M.O.H.s' Dinner.—The annual dinner of the Services Group of the Society of Medical Officers of Health will be held on March 14 at Simpson's Restaurant, 100, Strand, London, W.C.2, at 7 for 7.30 p.m. The cost per head will be 25s. (exclusive of wines). members may invite guests, and any serving officer will be welcome. Details may be obtained from Dr. G. M. Frizelle, London School of Hygiene and Tropical Medicine, W.C.1, who would like to be informed as soon as possible who will be present.

Royal Sanitary Institute Congress.—The annual health congress will be held this year at Margate from April 22 to 25. The fee will be £2 2s., but fellows, members, and associates of the Institute will be supplied with tickets free on application to the secretary, from whom full details may be obtained at 90, Buckingham Palace Road, S.W.1.

Study of Fertility.—The annual meeting of the Society for the Study of Fertility will be held in the meeting-house of the Zoological Society of London on June 27 and 28. Further information may be obtained from Dr. G. I. M. Swyer, Obstetric Hospital, University College Hospital, Huntley Street, London, W.C.1.

Association of Surgeons.—The annual meeting of the Association of Surgeons of Great Britain and Ireland will be held in Cardiff from April 17 to 19 inclusive. The full programme will be circulated in March, and all inquiries should be addressed to the honorary secretary, 45, Lincoln's Inn Fields, London, W.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday

FACULTY OF RADIOLOGISTS.—We very much regret that an error was made in our announcement (February 16, p. 394) of the meeting of the Radiodiagnosis Section on February 22. There will be no meeting on this date.

Sunday

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Adolph Tuck Hall, Woburn House, Upper Woburn Place, London, W.C., February 24, 3 p.m., "*Chemotherapy of Tuberculosis*," by Professor J. M. Robson.

Monday

EDINBURGH UNIVERSITY: FACULTY OF MEDICINE.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, February 25, 5 p.m., "*Steroid Hormones and Behaviour: Experimental and Clinical Aspects*," by Professor Marc Klein (Strasbourg)

HUNTERIAN SOCIETY.—At Mansion House, London, E.C., February 25, 8.30 p.m., "*P.P.S.*," Hunterian Oration by Dr. George Day.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—February 25, 5.30 p.m., lecture-demonstration for postgraduates by Dr. E. Stengel.

LONDON UNIVERSITY.—At University College, Physiology Theatre, Gower Street, W.C., February 25, 5 p.m., "*Antidiuretic Effects of Blood and Urine in Relation to Neurohypophysial Secretion*," special university lecture in pharmacology by Professor H. B. van Dyke (Columbia University).

MANCHESTER MEDICAL SOCIETY.—February 25. (1) At Lecture Room, Manchester Dental Hospital, meeting of Section of Odontology, 5 p.m., "*The Price of Medical Progress*," by Dr. A. Morgan Jones; (2) At Physiology Theatre, Medical School, Manchester University, meeting of Section of General Practice, 9 p.m., "*Tuberculosis and the General Practitioner*," by Dr. Marc Daniels.

Tuesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., February 26, 5.30 p.m., "*Research on Ageing*," by Professor E. C. Dodds, F.R.S.

EDINBURGH UNIVERSITY.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, February 26, 5 p.m., "*The Chemistry of the Adrenal Cortical Hormones*," Cameron Prize Lecture by Professor Tadeus Reichstein (Basle).

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—February 26, 5.30 p.m., "*Leprosy*," by Dr. R. G. Cochrane.

LONDON UNIVERSITY.—At Westminster Medical School, Horseferry Road, Westminster, London, S.W., February 26, 5.30 p.m., "*The Pathology and Treatment of Portal Hypertension*," special university lecture by Professor Milnes Walker.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—February 26, 5 p.m., "*Partial Nephrectomy in the Treatment of Renal Calculi*," Hunterian Lecture by Professor H. H. Stewart.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, London, W.—February 26, 5.30 p.m., neurological demonstration by Dr. C. Worster-Drought.

Wednesday

CAMBRIDGE UNIVERSITY.—At Department of Physical Chemistry, Free School Lane, Cambridge, February 27, 12 noon, "*Some Aspects of the Physical Chemistry of Amino-acids, Peptides, and Proteins*," by Professor John T. Edsall (Harvard University).

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—February 27, 5.30 p.m., "*Histopathology of Leprosy*," by Dr. R. G. Cochrane.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., February 27, 4.30 for 5 p.m., "*Differential Diagnosis of Frequency of Micturition*," by Mr. Harland Rees.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, Cavendish Square, W.—February 27, 8.30 p.m., "*The Surgery of the Heart and Great Vessels*," Second Lettsomian Lecture by Mr. R. C. Brock.

●ROYAL SOCIETY OF ARTS, John Adam Street, Adelphi, London, W.C.—February 27, 2.30 p.m., "*The Work of the National Research Development Corporation*," by the Right Hon. the Earl of Halsbury, F.R.I.C., F.Inst.P.

Thursday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., February 28, 5.30 p.m., "*Lability of Blood Pressure*," by Professor M. L. Rosenheim.

CENTRAL MIDDLESEX HOSPITAL, Acton Lane, Park Royal, London, N.W.—February 28, 10.15 a.m., clinical meeting open to all consultant physicians in area of North-west Metropolitan Regional Hospital Board. Details from Regional Adviser in Postgraduate Medical Education, 2, Gordon Square, London, W.C.1.

GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY, The Union, University Avenue, Glasgow.—February 28, 7.30 p.m., address by Sir Geoffrey Jefferson.

●INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—February 28, 5 p.m., "*Plastic Surgery*," by Mr. D. N. Matthews.

INSTITUTE OF PHYSICS: MIDLAND BRANCH.—At The University, Edgbaston, Birmingham, February 28, 5 p.m., "*Some Applications of Physics to Medicine*," by Professor F. W. Spiers.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—February 28, 4.30 p.m., lecture-demonstration in psychiatry by Dr. D. Curran.

ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY, Lisle Street, Leicester Square, London, W.C.—February 28, 4.15 p.m., demonstration and discussion of clinical cases; 5 p.m., "*Leprosy*," talk by Dr. R. G. Cochrane.

UNIVERSITY COLLEGE, Physiology Theatre, Gower Street, London, W.C.—February 28, 4.45 p.m., "*Mitochondria and Biological Oxidations and Phosphorylations*," by Dr. A. L. Lehninger (Chicago).

Friday

CHURCHES' COUNCIL OF HEALING.—At Alliance Hall, Palmer Street, Westminster, London, S.W., February 29, 7 p.m., "*The Vision of the Future*," by Dr. E. E. Claxton (Assistant Secretary, B.M.A.).

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—February 29, 5.30 p.m., "*Leprosy*," clinical demonstration by Dr. R. G. Cochrane.

●INSTITUTE OF DISEASES OF THE CHEST AND INSTITUTE OF CARDIOLOGY.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., February 29, 5.30 p.m., "*Surgical Aspects of Patent Ductus Arteriosus and Coarctation*," by Sir Clement Price Thomas.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, London, W.—February 29, 7.30 p.m., general meeting. "*What is the Value of the G.F.T.?*" by Dr. F. R. Curtis. A discussion will follow.

OXFORD UNIVERSITY.—At Magdalen College, Oxford, February 29, 5 p.m., "*The Neurophysiological Basis of Mind*," Waynflete Lecture by Professor J. C. Eccles, F.R.S.

ROYAL INSTITUTION, 21, Albemarle Street, London, W.—February 29, 9 p.m., "*The Brain as a Machine*," by Sir Henry Cohen.

UNIVERSITY COLLEGE, Physiology Theatre, Gower Street, London, W.C.—February 29, 5.30 p.m., "*Cell Physiology and Pharmacology—Some Cytochemical and Cytological Aspects of Drug Action*," by Professor J. F. Danielli, D.Sc.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Du Heaume.—On February 7, 1952, at the Windsmill Nursing Home, Enfield, to May (formerly Giffin), wife of Brian Du Heaume, M.B., B.S., 21, Bycullah Road, Enfield, Middlesex, a son—Alan.

Levy.—On February 13, 1952, to Enid (formerly Glyn), wife of Dr. Basil Levy, of Liverpool, a son—Peter.

MARRIAGES

Campbell—Stewart.—On February 9, 1952, in Manchester, Ross Campbell, A.M.I.C.E., of Warrington, to Diana Stewart, M.B., Ch.B., of Lancaster.

Heumann—Howells.—On February 9, 1952, at St. James's Church, Muswell Hill, London, N., Paul Clifford Heumann, B.A., to Désirale Howells, M.R.C.S., L.R.C.P.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Choose Your Analyst

Q.—*A patient has been recommended psycho-analysis. Relatives are anxious that he should have an Adlerian rather than a Freudian analysis. What, briefly, are the main differences? What other forms of analytical treatment are available?*

A.—The main practical difference between an Adlerian and a Freudian analysis is in the time involved, a Freudian analysis commonly taking two years or more, an Adlerian analysis seldom requiring more than a year. There are very wide differences between Adlerian and Freudian theories, and in the sort of interpretations which will be made by analysts of the two kinds to the patient. Adlerian theory is simpler and easier to understand, and relates most psychiatric symptoms to repressed feelings of inferiority, often associated with some particular part of the body. It is, as a rule, much more important to choose the right psychotherapist than to bother about the school he belongs to; the general practitioner should try to find a therapist who has plenty of common sense and will try to get practical results, rather than one who is hidebound in theory. Apart from Adlerian and Freudian analysis, there is also Jungian analysis; and there are psychotherapists who are eclectic, who make use of elements from all three types of theory, or who rely on explanation, persuasion, suggestion, and other methods which are the specific property of no dogmatic theory.

Judo Neck-strangle

Q.—*What is the mechanism of the Judo neck-strangle? This is sometimes used as a "hypnotic trick," and death can occur through vagal inhibition. I understand that Judo experts have some method for reviving those rendered unconscious by this strangle, such as striking a thoracic vertebra sharply with the knee.*

A.—The neck-strangle used in Judo is considered to act by compressing the common carotid arteries, so temporarily depriving the brain of its blood supply. Whether it ever acts by stimulation of normal or over-sensitive carotid bodies is not known: as the function of the carotid bodies has only recently become known to the medical profession and is not yet clearly and completely understood, further research would be needed to decide whether the unconsciousness produced by the neck-strangle is partly or entirely or occasionally due to stimulation of this kind. The time taken to produce unconsciousness would suggest that it may occasionally be so. No fatal case seems to have been reported over many years in Japan or elsewhere, and the process of being strangled in this way is not in any way painful. It often occurs when one is resisting a strangle, apparently successfully, and one may find oneself powerless to tap (recognized signal of defeat) by the time one realizes that the strangle has been effective.

In practice the Judo hold is simple enough but easier to demonstrate than to explain on paper; generally the supinated forearms are crossed, the fingers (not thumbs) inserted deeply behind the collar of the jacket as far back as possible, the thumbs on the outside of the collar or lapel helping to keep the collar secure: a scissors action of the forearms brings the radial edges against the neck just below the mandible, and increasing pressure compresses the arteries: there are, of course, variants of the technique.

In ordinary practice one taps when the pressure is correctly applied in the first instance; strangulation is rarely produced and, if so, is usually involuntary, as described above.

"Kuatsu," or the resuscitation of unconscious people, has many techniques, and these are taught only to instructors who have achieved the level of Black Belt: "striking a thoracic vertebra sharply with the knee" could be a rather crude description of one of the techniques that may be used. These techniques have not been put on paper because inexperienced and irresponsible people might indeed resort to striking a thoracic vertebra with the knee to the grave risk of the sporting population. Generally, they are sharp—but carefully graduated—taps on the spine, epigastrium, or one or two other points whose effects have been investigated empirically over a long period. They seem to produce reflex stimulation which may stimulate an individual who is unconscious in the way that—and under the conditions where—any counter-shock may do so. Whether they have any other virtues or efficacy, or can revive those who do not react to Western methods of resuscitation by injection, etc., I cannot say. So far as I know the matter has never been investigated scientifically.

Notification of Pemphigus Neonatorum

Q.—*Is pemphigus neonatorum a notifiable disease? I understand a midwife in domiciliary practice has to notify it to the supervising authority. What is the duty of the doctor in these cases? Also, what is the duty in this respect of an obstetrician in charge of a maternity hospital (a) in England, and (b) in Scotland?*

A.—Pemphigus neonatorum is not a statutorily notifiable disease like diphtheria or scarlet fever. Under the rules of the Central Midwives Board, however, and possibly also on instructions issued by the local supervisory authority, it is incumbent on the midwife who recognizes any abnormality, including pemphigus, in an infant under her care (*a*) to summon medical aid, after which the doctor called in attendance becomes responsible for the treatment of the case, and (*b*) to notify the local supervisory authority, which then takes the responsibility for investigating the circumstances of the case and dealing with the midwife. When a case or cases occur in a maternity unit the medical officer in charge is ordinarily responsible for control measures, but he will usually find it expedient to notify the medical officer of health of the local sanitary authority and get his co-operation.

As pemphigus neonatorum is not notifiable in either England or Scotland the same procedure should be adopted in both countries.

Proprietaries for Asthma

Q.—*Is it justifiable to prescribe on E.C.10 proprietary remedies for asthma which are substantially the same as the National Formulary neb. adrenal. et atrop. co.? Some of my asthmatic patients find the proprietary products more helpful.*

A.—There are minor differences in composition between proprietary preparations and the *National Formulary* neb. adrenal. et atrop. co. It is a common experience for patients to state that the *National Formulary* preparation is less effective than one or other of the proprietary preparations. Although it is difficult to exclude with certainty the suggestion that psychological factors play a part, in the writer's experience this is improbable, because in many cases patients have thought they were receiving an identical product. It is easy to recognize the difference between these preparations when given "blind" to patients. On the whole, therefore, I consider that it is justifiable to prescribe the proprietary remedies on E.C.10 when a patient states that they are definitely more effective than the *National Formulary* preparations in his case.

Brimstone and Cancer

Q.—*What are the medical causes of a taste and smell of sulphur? This was a leading symptom in a woman with cancer of the breast. The symptom disappeared about three weeks after radical mastectomy, but has now recurred; so far there is no evidence of recurrence of the growth. Is there any possible association between the cancer and the taste of sulphur?*

A.—There appear to be no references in the literature to an association of cancer with a taste of sulphur. L. S. P. Davidson (*Lancet*, 1949, **2**, 197) refers to the odour of mercaptan in the breath of patients with severe liver disease. H. G. Crabtree (*Cancer Res.*, 1946, **6**, 553) refers to evidence of a direct association between sulphur compounds in the cells and carcinogenic substances during the early stages of carcinogenesis; this association may be related to the normal process of detoxication, and may play a part in carcinogenesis.

Geographical Tongue

Q.—*What are the causes and treatment of geographical tongue?*

A.—Geographical tongue is a description applied to the appearance of bald patches on the tongue due to exfoliation of the surface horny layer. The patches may coalesce in a discoid pattern resembling alopecia areata of the scalp, and like this condition are functional in origin. Geographical tongue may occur alone or in association with functional dermatoses, especially of the exudative type such as urticaria, eczema, and seborrhoeic dermatoses. The condition is of no significance, it is usually symptomless, and like the accompanying dermatological ills is not responsive to any line of treatment; it may wax and wane or clear up completely.

NOTES AND COMMENTS

Seasickness.—Dr. GILBERT DALLEY (London) writes: I must take issue with your correspondent writing on seasickness ("Any Questions?" January 5, p. 57) who maintained that antihistamine-like drugs were less effective than hyoscine. I am not a sufferer myself, but from experience in small boats I can assure your readers that, if they wish to have a comfortable sea trip with all their faculties unimpaired, drugs such as "dramamine" or better still "avomine" are far preferable to hyoscine, and those who are sufferers from *mal de mer* will be able to enjoy going to sea.

OUR EXPERT writes: Dramamine is the 8-chlorotheophyllinate and "benadryl" the hydrochloride of diphenhydramine; the pharmacological action of dramamine and benadryl is the same (M. Nickerson, *Science*, 1950, **111**, 312). Equally the pharmacological action of avomine (promethazine-8-chlorotheophyllinate) and "phenergan" (promethazine hydrochloride) is the same. Experiments performed in small boats and designed to exclude personal prejudice (E. M. Glaser and G. R. Hervey, *Lancet*, 1951, **2**, 749) have shown that hyoscine is a better seasickness remedy and no more toxic than either benadryl or phenergan. The patients in these experiments took each drug in turn but did not know what drugs were used, and they preferred hyoscine.

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